A WORKBOOK FOR TECHNICAL TRAINING

Biosafety and Risk Assessment in Agricultural Biotechnology

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Ms. Koch's current work is centered on issues concerning the safety of genetically modified organisms. During the 1990s she worked with government task teams on the development of South Africa's GMO Act and the attendant regulations, and South African position papers for the International Biosafety Protocol negotiations and for the Codex Alimentarius Commission relating to food labeling. She is the chairperson of the AfricaBio working group on Biotechnology Education and Training and editor of the monthly electronic newsletter *BioLines*. Ms. Koch has organized nine regional biosafety training workshops in Africa and been an invited speaker at numerous international biosafety training workshops. Her publications include papers, book chapters, biosafety workbooks, and biotechnology directories; to date, she has been commissioned to prepare four situation analyses of biotechnology in South Africa and three analyses of biosafety in developing countries.

PART ONE

Biosafety in Principle and in Practice

"It is a maxim universally agreed upon in agriculture, that nothing must be done too late; and again, that everything must be done at its proper season; while there is a third precept which reminds us that opportunities lost can never be regained."

• Pliny the Elder (A.D. c. 23—A.D. 79), *Natural History* •

1 Introduction

Rationale and Objectives

Biotechnology is a complex topic that embodies difficult technical, social, and economic issues played out against a backdrop of human hunger, economic marginalization, and environmental degradation. Adoption of crops and agricultural products improved through modern biotechnology has proceeded slowly in developing countries, where the context for their use tends to be an uncertain mixture of welcome and resistance. From the start, the development and deployment of genetically modified organisms (GMOs) and genetically modified (GM) products has been cast as a proposition with high stakes. Proponents promise solutions to intractable problems in agricultural production and human dietary needs, and opponents warn of unsafe food and environmental disaster.

Where inadequate and irregular supplies of food limit standards of living, those who see genetic engineering technology as holding great promise for improving lives anxiously await the arrival of GM seeds for local farmers. At the same time, those who see modern biotechnology as an icon for corporate exploitation of the defenseless and the possible cause of environmental degradation, if not destruction, label GMOs and the products made from them as the seeds of inequity and ruin. Our view is that biotechnology is a powerful and valuable tool that provides both new strategies to address long-standing problems and new considerations regarding its safe and appropriate use. This workbook is written with the basic assumption that when and where biotechnology is embraced, knowledge and education will allow it to be used safely.

Considerable international, regional, and national effort has been expended to pave the way for this new technology's benefits to reach farmers and consumers. Assistance programs use a variety of approaches to support developing countries to draft national biosafety regulations and build capacity to establish and operate national biosafety systems. Seminars and consultations are held to highlight the need for appropriate government policies. Educational conferences and workshops raise government leaders' awareness of the potential benefits as well as environmental and food safety concerns associated with biotechnology. Technical training for conducting biosafety reviews builds capacity in this critical area of biosafety implementation. All of these efforts are directed towards a common goal: to support developing countries in taking responsible decisions regarding the introduction of GMOs into the environment and the marketplace.

The lack of biosafety capacity in developing countries is a major constraint to the transfer of this technology, as public and private sector research organizations await a clear regulatory environment through which to bring their products to the grower and consumer.

Successful regulatory implementation requires the capacity to conduct safety assessments to ascertain whether a proposed use of a particular GMO presents an unacceptable risk to the environment or human health. Such biosafety reviews are conducted to provide a scientific basis for decisions regarding:

- Requests from companies seeking to import and sell GM seed or planting material
- Applications to field test transgenic materials developed locally or by donor-funded programs and/or multinational companies
- Approval for importation of GMOs as commodities or for research and testing purposes
- Requests for authorization to produce or grow GMOs on a large scale or for commercial purposes

In some countries the development of GMOs in contained facilities (laboratories) and the movement of GMOs between facilities are also regulated.

The task necessitates training for members of national and institutional biosafety review committees, who typically have little or no experience with biosafety issues or evaluations. In this workbook we address the technical aspects of biosafety review. We provide extensive background information as well as guided, hands-on practice in applying risk-assessment and risk-management procedures using a case study approach. In practice, such training will strengthen the quality of biosafety committee recommendations and decisions. Specific objectives of this workbook are to:

1. Provide a structured framework for a technical training program aimed at biosafety reviewers
2. Build the competence and confidence necessary for reviewers to conduct science-based reviews leading to appropriate decisions
3. Provide instructional materials to support ongoing training conducted by local organizations

The focus of this workbook is on genetically engineered agricultural crop plants. However, most of the material is relevant to GM ornamental and tree species, with some applicability to GM micro-organisms.

Audience

This workbook is designed to complement technical biosafety-assessment training courses in developing countries. We provide a background for the practical application of biosafety review procedures using a case study approach.

Our intended audience for such training includes members of national biosafety committees, biotechnology regulatory officials, and scientists working in the public and private sectors. Independent of a training course, the workbook itself may be a useful resource for national decision-making bodies, government regulators in related areas, and those charged with monitoring approved field-test releases. In addition, the workbook can serve as a resource for university and postgraduate students who have an interest in the responsible use of biotechnology for developing improved agricultural crops, trees, ornamental plants, and products derived from them.

Organization

This workbook is organized in three parts. Part One: Biosafety in Principle and Practice comprises background and instructional material organized in six sections. Following the purpose and rationale for creating the book, the intended audience, and the organization of the book, section two presents the context for biosafety assessments, the resources necessary for conducting them, and the process that supports regulatory decision making. Section three covers risk assessment and the environmental and health issues associated with products of agricultural biotechnology. Section four presents risk-management principles and applications. Monitoring is discussed in section five and risk communication, the art and skill of sharing information among interested parties, is covered in section six.

Part Two is the "working" part of the workbook — a collection of case study exercises that entail use of risk-assessment, risk-management, and risk-communication procedures by training course participants. The cases are based on applications submitted to national biosafety review committees; we have modified them to be suitable as classroom exercises. This edition contains two applications for greenhouse research, two for field testing, one for commercial release (placing on the market), and one for GM commodity import. During a training course, students will gain practical experience by evaluating applications under the guidance of experienced instructors.

Part Three contains supplemental information relevant to the text and case studies. Appendix I is a Glossary of Terms. Appendix 2 is an Annotated List of Internet Sites providing additional information. Appendix 3 is a list of Sources and Suggested Reading.

We are preparing a separate instructor's manual to facilitate subsequent training sessions conducted by local instructors. The instructor's version will include supplemental information, materials on additional topics that may be of interest, notes, supplements and guidance questions for case studies, pages to be made into transparencies, and the like.

2 Context for Biosafety Review and Decision Making

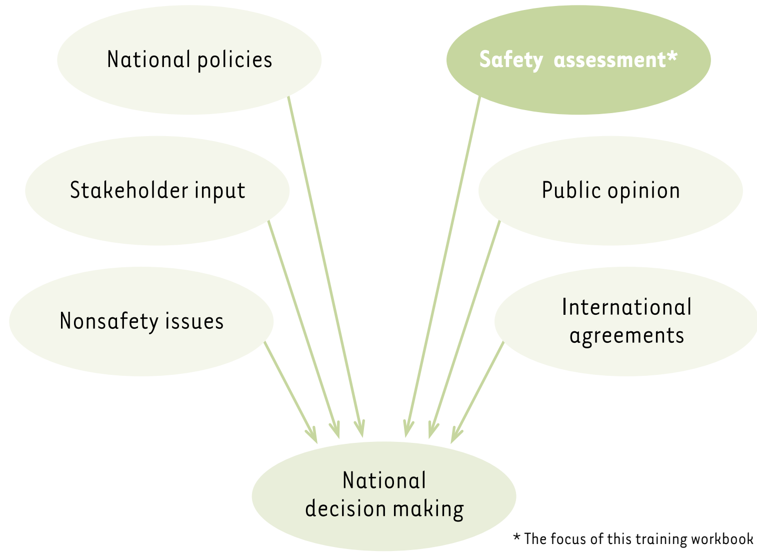
Biosafety review — the scientific evaluation of a GMO's potential effects on the environment and human and animal health — is often seen as the single factor that determines whether or not a GMO or product is approved for testing or use. However, safety assessments are conducted within a larger context for decision making that includes national policies for agriculture, biotechnology, and biosafety (or lack thereof), international agreements, stakeholder interests, and public attitudes (see Figure 1).

Factors Affecting Decision Making

Countries individually decide whether to develop, deploy, or use genetically modified organisms and the products made from them. Such decisions take into account national policies for agricultural research and development and the potential role of biotechnology in meeting national goals and objectives in food production, food security, trade, and related areas. Decisions regarding the use of this technology and its products are based, in part, on a determination that they do not pose an unacceptable risk to the environment or to human health.

With the pending entry into force of the Cartagena Protocol on Biosafety to the Convention on Biological Diversity (the Cartagena Protocol)[1] — a legally binding international protocol for the safe transfer, handling, and use of living modified organisms — such biosafety assessments soon will become part of international trade agreements. Other factors not related to environmental or health safety are typically considered in national decisions regarding the use of GM crops, organisms, and the products derived from them. Among these are social and economic considerations, requirements under national law and international agreements, stakeholder input, ethical issues, and impacts on trade. These nonsafety factors, significant in terms of public acceptance, are rightfully considered in decision making by competent authorities. However, this workbook is focused more on the technical aspects of scientific biosafety review; we do not attempt to address nonsafety factors fully here.

Figure 1. Factors governing decisions about the release and use of GMOs. Factors in decisions about the release of a GMO are based in part on safety assessment and necessarily include other considerations as well. Nonsafety issues such as effects on society, economic consequences, and effects on trade are also keys in decision making. Typically, decision making incorporates, whether formally or informally, stakeholder input, public concerns and opinions, existing policies in agriculture, the environment, and food safety and responsibilities under international agreements.



National Policy

A strong national policy environment for agriculture, new technologies, resource conservation, and related areas will foster the adoption of appropriate GM technologies. Coherent policies promote development of an implementable regulatory system for biosafety and guide its coordination with related regulatory mechanisms (e.g., phytosanitary requirements, seed registration, etc.). They provide a basis for accommodating the differing interests of ministries of agriculture, health, science and technology, environment, or others involved. Weak or absent national policy, in contrast, may serve as an impediment to technology transfer and adoption.

Around the world, national policies on genetic modification differ significantly in their objectives. Some countries design policy to protect the environment and human health against uncertain or unidentified risks, allowing use of the technology only to the extent that its impacts are known or can reliably be predicted. Others frame policy to encourage the introduction of technologies that will benefit the country and its people, striving to identify and manage actual or potential risks, to the extent possible given current knowledge, and to balance these against the status quo.

Policy decisions regarding the relative roles played by the various ministries involved shape biosafety implementation. The statutory nature of biosafety regulations, whether issued as law, by ministerial decree, or as advisory guidelines, will dictate the nature and extent of enforcement measures and the means for addressing noncompliance. Existing regulatory agencies, such as those for plant quarantine and seed registration, may have statutory authorities that apply to GMOs and that need, therefore, to be coordinated with biosafety regulation.

International Agreements

At least three international agreements — the Cartegena Protocol on Biosafety, Codex Alimentarius, and the International Plant Protection Convention — pertain to biotechnology development and trade. This fact indicates that a wide and complex scope of regulatory issues are associated with the use of the technology.

Cartagena Protocol on Biosafety

The Cartagena Protocol on Biosafety (CPB) is a legally binding international agreement negotiated under the auspices of the 1992 Convention on Biological Diversity. Its primary aim is to protect biodiversity by ensuring the safe and responsible "development, handling, use, transfer and release of any Living Modified Organism." The protocol addresses transboundary movement of living GMOs; it also applies to the use or trade of products derived from GMOs, such as grain processed into meal or flour, cotton fiber or seedcake, vegetable oils, or any processed food. Under the terms of the

The Precautionary Principle as Stated in International Documents

"Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation."

— Rio Declaration on Environment and Development ("Earth Summit"), 1992, Principle 15

"Lack of scientific certainty due to insufficient relevant scientific information and knowledge regarding the extent of potential adverse effects of a living modified organism on the conservation and sustainable use of biological diversity in the Party of import, taking also into account risks to human health, shall not prevent that Party from taking a decision, as appropriate, with regard to the import of the living modified organism . . . in order to avoid or minimize such potential adverse effects."

— Cartagena Protocol on Biosafety, 2000, Articles 10.6 and 11.8

"In cases where relevant scientific evidence is insufficient, a Member may provisionally adopt . . . measures on the basis of available pertinent information . . . (I)n such circumstances, Members will seek to obtain the additional information necessary for a more objective assessment of risk and review . . . the measure accordingly within a reasonable period of time."

— World Trade Organization 1993 Agreement on Application of Sanitary and Phytosanitary Measures, Article 5.7

CPB, exporting member countries must obtain an advance informed agreement for GMO importation before shipment. Such agreement is conditioned on the recipient country's performance of both an environmental risk assessment and food-safety assessment. The CPB includes guidelines for assessing environmental impact and provides for a central clearinghouse of information on GMO production, export, and biosafety data.

Countries that sign the protocol assume certain responsibilities with respect to the use of living GMOs. They are obliged to designate a focal point for liaison with the CPB secretariat and one or more competent authorities to carry out the assessment provisions of the protocol. These include development and implementation of regulations to manage the safe use of living GMOs. In practical terms, this entails a review and modification of existing legislation or drafting of new legislation, infrastructure development, and strengthening of biosafety review capacity within the government and scientific communities.

Codex Alimentarius

The Codex Alimentarius Commission is an international working group that sets standards for food safety, quality, and labeling. It functions under the Food and Agricultural Organization (FAO) in Rome. The Codex *Ad Hoc* Intergovernmental Task Force on Foods Derived from Biotechnology was formed to develop standards, guidelines, or recommendations, as appropriate, for foods derived from biotechnology or traits introduced into foods by biotechnology. The final report is due at the twenty-fifth session of the commission in 2003.

In the interim, work on international guidelines for the labeling of GM foods is progressing; a draft was made available in 2002. Signatories to the Codex will be required to bring their national labeling legislation into line with the new Codex labeling guidelines when these enter into force.

International Plant Protection Convention

The International Plant Protection Convention (IPPC) is a multilateral treaty deposited with the director-general of the FAO and administered through the IPPC Secretariat located in FAO's Plant Protection Service. The purpose of the IPPC is to secure common and effective action to prevent the spread and introduction of pests of plants and plant products and to promote measures for their control. The convention provides a framework and forum for international cooperation, harmonization, and technical exchange in collaboration with regional and national plant protection organizations. The IPPC plays a role in trade because it is recognized by the World Trade Organization in the Agreement on the Application of Sanitary and Phytosanitary Measures (the WTO-SPS Agreement) as the source for international standards for the phytosanitary measures affecting trade. It therefore will affect the export and import of biotechnology products.

Stakeholder Involvement

Stakeholders in biosafety decision making are those interested in or affected by decisions regarding the use of GMOs. In addition to scientists and research directors, the term encompasses farmers and farm organizations, environmental groups, local landowners, consumer organizations, industry and trade organizations, seed suppliers, national and local authorities, and the like. Stakeholders and decision makers share the common goal of using biotechnology and GM products in such a way as to derive benefits that sufficiently outweigh potential detriments. The same can be said for the use of any technology, whether it is automobiles, vaccines, or electricity.

Stakeholder input is critical in drafting biosafety regulations and laws that are realistic and implementable and that take into account the most current credible information. Stakeholders can provide critical input into setting research priorities that focus on primary constraints in agriculture and food supply for which biotechnology is the most appropriate approach. They are also in a position to promote compliance with regulatory requirements and implementation of management plans (e.g., farmers charged with field surveillance).

Public Input

The general public cannot have confidence in official statements that assert "this GM crop is safe to grow and safe to eat" if they feel deliberately excluded from the decision making. Needless to say, opponents of biotechnology are aware of this, too, and easily raise suspicion and fears by claiming that the public has no voice in decisions regarding the use of GM technology. Furthermore, perceptions that biosafety reviews are inadequate, that deliberations are conducted behind closed doors, and that private sector interests are strongly influential seriously undermine the credibility of biosafety reviewers and competent authorities.

With few exceptions, *technical* biosafety reviews are primarily scientific evaluations conducted by a small group of specialists and, usually, government officials. Final decisions about consumers' use of GMOs, however, must necessarily consider both safety and nonsafety (e.g., socioeconomic, trade, equity) issues. It is at this point that public input should become a factor in decision making.

Public participation in biosafety decision making, specifically addressed in Article 23 of the Cartagena Protocol, typically is achieved through mechanisms to solicit public comment on proposed activities and pending decisions on GMO market releases and deliver it to decision makers. National biosafety officials may use normal government communications channels to announce such events and call for public comment. In a few cases, even proposed field tests are open for public comment. Regulatory officials may place notifications and contact information in local newspapers and on radio programs or conduct local informational meetings. Public meetings are especially useful in that they allow diverse points of view to be heard. The discussions sensitize scientists and regulators to public concerns and at the same time provide an opportunity for the public to obtain accurate information. (See section six, "Communicating about Risk and Biosafety.") A few countries (e.g., the Philippines and the United Kingdom) have instituted direct public involvement in biosafety assessment of GMOs by including representatives of the general public on their national biosafety committees. These committee members may or may not have a technical background.

Terms of Reference for Biosafety Committees

Groups best work together when members have a common understanding of the group's purpose, scope of subject matter, and mode of operation. Ideally, such information for national biosafety committees is specified in formal or informal terms of reference. Although few committees in developing countries have written terms of reference (and many in developed countries lack them as well), they can be instrumental in setting up a functional and effective biosafety committee and serve to coordinate its operations within the larger national regulatory framework.

Terms of reference (principles of operation) are often the first level of guidance for a biosafety committee. They may be articulated within national regulations, guidelines, rules for implementation, or as a separate document. They may address a range of topics, several of which are listed in the box below. Usually, terms of reference establish how the committee is to function, the boundaries of activity in which it may be involved, and the expectations for its deliberations and output. The choice of topics to include and the language used to describe them will reflect the regulatory framework and the perspectives of those drafting the terms. In practice, the list would be longer, perhaps including such additional topics as document management and record keeping, committee procedures, handling of confidential business information, review procedures, member confidentiality, use of external

Terms of Reference for Biosafety Committees: Topics and Samples

The terms provided for each topic are examples of how each topic could be addressed; many other approaches are possible.

PURPOSE

A. The National Biosafety Committee (NBC) is constituted to conduct scientific reviews of applications to import, field test, produce, and/or place on the market genetically modified organisms (GMOs).

B. The NBC is the competent authority for determining the acceptability of a GMO intended for local consumption as food, feed or fiber, export or trade, production of industrial or pharmaceutical products, or any other applications, on the basis of a scientific evaluation of risks, benefits, and comparison of these with those of their conventional counterparts.

C. The Biosafety Advisory Group serves in an expert capacity to evaluate the potential risks of GMOs to human health and the environment and make recommendations to the Ministry of the Environment regarding their use and distribution.

AUTHORITY

A. The NBC is constituted under authority of the Minister of Agriculture as assigned in the Agricultural Products Use Act of 1999.

B. In accordance with Environmental Protection Directive 86-041, as amended on 3 June 1991, the Council for the Environment will establish, maintain, and provide support to an NBC.

APPOINTMENT

A. Members of the NBC will be appointed by the Deputy Minister of the Environment upon recommendation by the Secretary of the National Council of Environmental Affairs.

B. The Director of Agricultural Development and Trade will receive nominations for membership annually. After formal screening, selected individuals will be invited to sit on the committee for a term of 5 years.

C. Members are appointed by the Deputy Director of Agricultural Research and Development. In addition, the President may at any time appoint an additional member or members of his/her own choosing.

MEMBERSHIP

A. The committee is composed of scientists having expertise in relevant scientific disciplines, including molecular biolor *ad hoc* advisors, and dealing with conflicts of interest. Each country or committee must formulate its own terms of reference according to its biosafety objectives, regulatory infrastructure, human resources, and similar contributing factors.

Note that some of the sample terms of reference are overly restrictive. An example is "Scope of Review: The committee's primary responsibility is to conduct a safety assessment of applications to field test or commercialize GMOs. Risks are to be identified, their magnitude estimated, and their potential negative consequences described." The wording confines reviewers to look only at risk. No balancing consideration is to be given to potential benefits or positive consequences.

In other cases, the terms are very broad. An example is "Membership: The committee is composed of scientists having expertise in relevant sci-

ogy, plant breeding, genetics, plant pathology, agronomy, weed science, ecology, and others.

B. Members include the Deputy Minister of Agriculture, Director of the National Council for Science and Technology, the Minister's science advisor, representatives of the Ministries of Environment, Health, Production and Trade, and scientists having expertise in disciplines.

SCOPE OF REVIEW

A. Biosafety reviews will focus on scientific issues related to environmental impacts of the proposed activity. Analyses will be based on scientific data provided by the applicant or by outside sources.
B. The NBC evaluation will focus on the potential risks and potential benefits of a particular GMO in light of the known risks and benefits of the nonmodified conventional variety.
C. The committee's primary responsibility is to conduct a risk assessment of applications to field test or commercialize GMOs. Risks are to be identified, their magnitude estimated, and their potential consequences described.
D. The Biosafety Advisory Board Review will, in the course of its assessment, consider the necessity for developing the GM variety, its relevance to national needs and priorities, and comparative advantages/disadvantages over non-GM varieties.
E. The NBC will not comment on the proposed experimental design or choice of scientific methods except where concerns are raised that safety could be compromised.
F. Nonsafety concerns (e.g., socioeconomic impact) will be referred to an auxiliary body established for that purpose or to the decision-making authority for independent evaluation.

POSTREVIEW RESPONSIBILITIES

A. The committee will be responsible for establishing a follow-up monitoring program for compliance with regulatory decisions and any constraints therein. This may be accomplished through submission by the applicant of annual reports or a final report, site visits by NBC member(s) or their representative(s), or as otherwise deemed sufficient by the committee.
B. After completion of each review, the committee or an appointed spokesperson will be available to the Deputy Minister of Agriculture to respond to follow-up questions or additional analyses as deemed necessary.

entific disciplines, including molecular biology, plant breeding, genetics, plant pathology, agronomy, weed science, ecology, and others." This term leaves open who makes the appointments, by what process, the number of members, and their length of service. Both strong and weak examples are given as a way to stimulate discussions of the merits, drawbacks, and, most importantly, the implications of each.

Additional terms of reference may address topics such as committee procedures, use of external or *ad hoc* advisors, record keeping, handling of confidential business information, and dealing with conflicts of interest.

Use of Prior Reviews

Applications for field tests or market releases in developing countries in many cases involve GMOs previously approved by national biosafety committees elsewhere in the world. The findings of these committees are a valuable resource because they can direct subsequent reviewers to specific areas of concern and indicate how these concerns might be addressed. Sharing documentation from prior reviews helps build familiarity with specific GM products, gives insight into management procedures, provides direction on additional information that may be needed for the current review or at later stages in the development process, and raises the confidence with which decisions are made.

The validity of conclusions from risk assessments conducted in other countries is limited, however, by the extent to which there are significant differences in environmental, ecological, and agronomic conditions. Existing biosafety data should be acceptable but are not necessarily sufficient for reviews conducted elsewhere, particularly in countries that are centers of origin or centers of diversity for certain crop species. Local experts will need to evaluate the available data. They may request that additional data pertaining to local conditions be provided before approval can be given or that additional safety data be collected during the field-testing phase of a GM product with commercial potential. Regional environmental similarities and crop preferences may allow neighboring countries to share biosafety data and collaborate on environmental risk assessments for the region. This approach offers advantages in sharing biosafety costs and expertise within the region and reduces duplication of effort, yet leaves decision making to national authorities.

To facilitate access to previous biosafety review data, the Secretariat for the Cartagena Protocol on Biosafety will provide a clearing house[2] for biosafety data that can be accessed by national scientific review and decision-making committees. This database will house information that addresses concerns about specific GM products in specific environments and methods to manage and monitor them. Parties to the protocol will be required to submit their biosafety information to the clearing house.

Decision Documents

Biosafety decisions typically are recorded in some form of decision document. The documents present key findings of the biosafety review committee and of other parties providing information and advice that collectively form the basis for a final decision to use, or not, a particular GMO in a specified way.

Decision documents prepared by biosafety committees serve to communicate their science-based findings to regulators, applicants, stakeholders, and interested parties. Such reports will:

- Summarize the application
- Note any information missing from the original application and steps taken to provide it to the committee's satisfaction
- Summarize the review process, discussions, and findings of the committee
- Detail the committee's recommendations in regard to their mandate
- Add additional comments (outside the immediate mandate of the committee and the scope of the present application) that regulators or the applicant may wish to consider in subsequent applications
- Outline the conditions under which an approved activity is to proceed, including required risk-management measures, reporting procedures in case of unexpected events, and record keeping

In contrast to the relatively simple safety assessments of field-test applications, requests for large-scale or commercial GMO production and/or marketing are subject to much more extensive review that includes factors such as long-term environmental effects, food-safety assessment, and nonsafety considerations. Accordingly, in addition to the findings and recommendations of the review committee, decision documents pertaining to commercial releases may incorporate:

- Findings and recommendations of the national food-safety committee
- Opinions given by *ad hoc* scientific experts as requested by the review committee (e.g., ecological studies)
- Findings of outside review teams charged with evaluating the social, economic, and trade impacts of the GMO
- A summary of input from the public
- Any combination of these depending on the structure of the advisory groups and their mandates

Decision documents serve to advise regulators and government officials and inform the public of how a decision was reached. As such, the language should be nontechnical — key words should be defined and all jargon eliminated. For transparency and accountability, documents should be signed by the review committee or competent authority.

Resource Requirements

Scientifically sound safety assessments and measures for handling GM crops, trees, and ornamental species and their products safely require human, financial, and information resources as well as an adequate infrastructure. Below we detail some of the specific resource needs.

Personnel

Scientists

Sound biosafety reviews require the expertise of scientists knowledgeable about the organisms, the introduced traits, and the environment into which specific GMOs will be released. The scope of disciplines relevant to biotechnology and biosafety is extensive. Some countries, such as the Philippines and China, have a large pool of qualified life scientists and thus are capable of securing the necessary expertise. Many others lack sufficient scientific capacity and will find it difficult, if not impossible, to assemble a properly constituted national biosafety committee.

Circumventions (not necessarily solutions) to this widespread problem include:

- Using experts drawn from neighboring countries
- Using international experts, consultants, or advisors
- Accepting biosafety assessment conclusions

reached by national review committees in other countries
- Establishing a regional biosafety system that pools resources to evaluate proposed field-test releases having regional relevance

In addition to basic scientific expertise, biosafety reviewers need skills in risk-assessment and risk-management procedures (see sections three and four). Those who will serve as inspectors and monitors of field-test releases need to understand the why, where, when, and how of field or facility inspection and monitoring (see section five).

Training programs can help build technical capacity; however, it takes time to build the competence and confidence of biosafety officials. Training should be an ongoing activity; attendance at one course, such as one based on this workbook, is not equivalent to being "knowledgeable and trained." For that, accumulated practice and hands-on experience are needed.

Managers

In the course of implementing biosafety, management responsibilities are commonly placed on people who have little or no prior experience in this area. New managers will need skills in:
- Priority setting
- Resource acquisition and allocation
- Coordination with multiple agencies
- Meeting management
- Communications across many sectors
- Information access and management
- Handling of confidential or proprietary information

Government Officials / Decision Makers

Political support, or its absence, is key to determining whether a functional biosafety system can be established and put into operation, or whether the effort falls short despite strong support at the institutional level and among scientists. Thus it is vitally important that ministry officials and their science advisors are well informed about the role of biotechnology in agricultural development and the role of the biosafety system in bringing beneficial products to all citizens.

Officials who have formal responsibility for biosafety and who make decisions on proposed field-test releases are, in essence, the gatekeepers who determine what biotechnology products, if any, will be allowed, and when. Those more directly involved in biosafety operations are potential allies in helping secure necessary financial resources. Those having regulatory authority set the pace for actual testing and commercial use. The cooperation and support of these people may, in fact, be the most important resource of all. Efforts to engage them and keep them as informed as possible are likely to be well worthwhile.

Scientific Expertise Used in Reviewing South Africa's First 150 Field-Test Applications

Molecular biology	Agronomy	Human health
Plant pathology	Pesticide usage	Biochemistry
Microbiology	Nutrition	Plant genetics
Plant taxonomy	Soil biology	Biocontrol
Fermentation	Ecology	Food safety
Pollination biology	Plant physiology	Weather
Veterinary science	Entomology	Law

Information and Access

Scientific biosafety review teams require a significant amount of information and data on which to base their recommendations. The greater the degree of confidence sought, or the lower the tolerance for an erroneous finding, the more information needed. Much of the necessary information may be supplied with the application. However, a predetermined set of questions may not elicit all that is necessary and sufficient to complete an informed risk assessment. Where gaps exist, or if supporting or confirming information is needed, review teams need access to other sources.

Sources

Information to support safety assessments and recommendations is available from a wide range of sources and in a variety formats: peer-reviewed scientific publications, experts in relevant professional fields (e.g., breeders, agronomists, seed suppliers), conference proceedings, review articles, and even colleagues working in local institutions. Decision documents from other national biosafety committees are a particularly rich source of information on identified risks and management options for particular GM crops and products.

The scientific literature is full of useful information, but persistence is often required to locate the right material. Biosafety-related information may be found in books and journals concerning:

- Basic knowledge of crop biology and agronomic practices
- Ecological relationships in agricultural systems including the crop, its pests and pathogens, and environmental conditions
- Major biotic and abiotic constraints to crop productivity
- Peer-reviewed experimental risk-assessment data and analyses
- Review articles on biosafety issues and current expert opinions on associated risks and risk-management procedures
- Regulations and guidelines from other countries
- Reports and documents from international organizations

To address the need for support in biosafety implementation, the Cartagena Protocol calls for an international biosafety clearing house to coordinate and disseminate information to member countries. The clearing house will be restricted to information about the deliberate transboundary movement of living modified organisms. Until it is set up, a number of research, educational, government, private sector, and civic organizations have attempted to make certain information more readily accessible. Appendix 2 is an annotated list of Internet sites providing useful information about agricultural biotechnology, basics of genetic engineering, benefits and potential risks, national regulations, the Cartagena Protocol, field tests and commercial products, and related topics.

Acquiring information

Information can be accessed through many channels. Books, journal subscriptions, participation in conferences and symposia, and personal networking have long been the mainstays of information transfer. These sources remain extremely valuable and should continue to receive institutional support. However, the world is in the midst of a rapid transition from paper-based to electronic forms of information. The Internet has overtaken other resources in terms of sheer volume of material. Internet-based and electronic information is much more difficult to obtain in countries where e-mail and Internet connections are unavailable, unreliable, or laborious. Accordingly, countries seeking to implement biosafety systems must give high priority to strengthening the communications infrastructure to provide adequate access to electronic information.

Misinformation

The Internet is without doubt the world's richest source of information; with a little skill in search methodology, information seekers can find practically any information they want. However, because the Internet is open to all and there is no mechanism for moderating its use or policing its content, the quality of information found there is highly variable, to say the least. There is no requirement for accuracy, honesty, or accountability. The situation is compounded by the widely held view that any information that is published is "true." Web site owners can post, move, alter, or remove content at will; original sources can be hidden or absent. This state of affairs brings a new responsibility to biosafety reviewers and decision makers: They must double check the accuracy of information from unknown or unaccredited Web sites before using or disseminating it. In this age of information overload, the ability to critically evaluate the quality of information and be appropriately selective is a skill of increasing importance.

Needed Resources

The expenses of obtaining information, maintaining libraries or data bases, and sorting and disseminating information are unavoidable. Funding must be secured for the necessary infrastructure (computers and communications equipment, reliable links for telephone, fax, e-mail, and Internet connections) and technical support. Information costs associated with conducting biosafety reviews may escalate in time as well as money if required data are unavailable and the only way to get them is through additional research. Striving to improve accuracy in biosafety reviews — by increasing the amount of information obtained or the robustness of the analysis performed — increases the cost of the enterprise and decreases the relative value of additional information. At some point, the value of additional information may not be sufficient to justify its cost. Decisions will need to be made about how much is enough and how available information will be used to best meet national biosafety needs.

Feedback Mechanisms

Field trials of GM varieties are carried out to collect data of commercial and biosafety importance. Feedback, in the form of data and information derived from prior GMO releases, helps support subsequent biosafety committee deliberations, particularly in the early phase of biosafety implementation. Feedback mechanisms can also provide information that may help improve procedures for future field tests. Extensive plantings of commercial GM crops provide unique conditions that may also result in new data. Requiring applicants to continue to collect specific data after market release enables ongoing monitoring of the crop's impact on the environment.

Many countries obtain feedback by requiring a report to be submitted at the end of a trial period. Taking the time to specify the data required in each field test report ensures that the relevant data are collected. Data collection after approval for commercial use can be requested as a condition of the authorization to commercialize.

Financial Support

Biosafety systems impose financial costs for implementation and for compliance.

Implementation Costs

Costs of establishing and operating a biosafety system include:

- Education of policy makers and stakeholders
- Development of regulations
- Development and distribution of procedural information
- Training for reviewers
- Administrative expenses of the biosafety review committee
- Salary and support for paid staff
- Pre-release site visits (if required)
- Inspections during and upon termination of the field-test release
- Follow-up monitoring
- Training for inspectors
- Documentation and record keeping

In some countries, applicants are charged fees to cover these costs. While this approach may be suitable for applicants from the private sector, where such costs are viewed as a normal part of doing business, applicants from national research institutes, universities, and other public sector organizations may find the costs prohibitive.

Compliance Costs

Compliance costs are those incurred by the GMO developer in meeting regulatory requirements. Included are expenses for:

- Generating data needed for the application
- Implementation of risk-management measures
- Post-release monitoring prescribed as a condition of approval
- Reporting and documentation

For GMOs that have undergone prior review in another country, requiring a complete replication of the data, particularly food-safety data, is a costly process difficult to justify. The financial outlay for collecting a new set of data may preclude some applicants from testing GM products.

3 Risk Assessment

Risk assessment is inherently the most critical component of biosafety implementation. Those who make determinations of the relative safety of a biotechnology product and its use will be well served to master an understanding of the approaches that have been used for assessment of environmental risk and the reality of what an assessment may or may not do. With some grasp of the basics, better choices of personnel, education, and training needs may be brought to the formation of biosafety committees and their implementation of regulations or laws.

To fully understand the concepts of risk assessment, it is necessary to have some comprehension of what it is and, as importantly, what it is not. A number of definitions have been offered. Each assumes a basis in or reliance on scientific information. In the broader view, risk assessment is a means for dealing with uncertainties and incomplete data in order that decisions may be made in full consideration of potential consequences. It is influenced by policy choices, individual experience, and public reaction.

Methodology for Biotechnology Risk Assessment

A generally accepted methodology for biotechnology risk assessment has been outlined in several easily accessible documents including the *UNEP International Technical Guidelines for Safety in Biotechnology*[3], the Cartagena Protocol[4], and EC Directive 2001/18/EEC[5]. Each of these include the following steps that, together, identify potential impacts and assess the risks:

1. Identify potential adverse effects on human health and/or the environment
2. Estimate the likelihood of these adverse effects being realized
3. Evaluate the consequences should the identified effects be realized (the risk)
4. Consider appropriate risk-management strategies
5. Estimate the overall potential environmental impact, including a consideration of potential impacts that may be beneficial to human health or the environment

At any point, more data may be needed to arrive at a final recommendation about whether the

Definitions of Risk Assessment

"... the attempt to quantify the degree of hazard that might result from human activities ... an exercise that combines available data on ... potency in causing adverse ... effects with information about likely ... exposure, and through the use of plausible assumptions, it generates an estimate of risk."

—William D. Ruckelshaus, 1985

"... the scientific activity of evaluating the potential effects of an entity and its application in order to ascertain the likelihood that an adverse effect may occur, and to characterize the nature of that effect."

—Paraphrase from National Research Council, 1983

"... the process of obtaining quantitative or qualitative measures of risk levels, including estimates of possible health and other consequences."

—V. T. Covello and J. R. Fiksel, 1985

"... an analytical tool that facilitates the organisation of large amounts of diverse data with the goal of estimating the potential risk posed by a process (or event) of interest."

—H. S. Strauss, 1991

"... the measures to estimate what harm might be caused, how likely it would be to occur and the scale of the estimated damage."

—United Nations Environment Programme (UNEP), 1996

activity can proceed with an acceptable level of safety. Thus the process may be "put on hold" until the needed information is provided.

Organizing the Scientific Information

The very large and ever increasing amount of scientific information available warrants consideration of structured approaches to risk assessment. Indeed, risk assessment requires a different way for scientists to organize and evaluate information. They are asked to evaluate a product's safety as opposed to its potential contribution to scientific knowledge.

In this brief discussion we highlight some of the important aspects of the thinking that has gone into developing such structured approaches. Although these appear disparate in nature, they are consistent with the goal of defining and quantifying potential risks or supporting the notion of "no foreseeable risk." In reality, no single approach is best; the one used typically is the approach most suitable to the needs of the present circumstances. Reviewers will find themselves using different approaches to different applications, or even to different sections of one application.

Over the years, many approaches to biosafety analysis have been used by regulatory scientists or proposed in the literature.

Trait Analysis Approach

In trait analysis, the assessor categorically evaluates attributes of (1) the parental organisms, (2) the genetic construct, (3) the modified organism, and (4) the environment in which the organism is to be released for testing. The analysis uses pertinent criteria and an indication of levels of concern dependent upon the attributes. For example, an organism with a short survival time would be of less concern than one with a long survival time.

Approaches to Risk Assessment

APPROACH	FOCUS	COMMENTS
TRAIT ANALYSIS	Characteristics of the modified organism including the transferred gene(s), the parental organisms, and the receiving environment	Works well when releases are small in scale, but becomes increasingly difficult and less certain as spatial and temporal scale increases
FAMILIARITY	Comparison of modified organism to similar organism(s) that is (are) well known and of GM traits to similar traits derived through classical genetic methods	Based on the assumption that "small" genetic changes (one to four genes) will result in no significant change in a well-known organism (e.g., crop plant) and that phenotypic expression is the same regardless of how the modification was obtained
FORMULAIC	Possible adverse effects (e.g., to the environment or human health) and the probability for their occurrence	Useful for organizing scientific information into two categories; facilitates consideration of risk-management options
INTUITIVE REASONING	What is known or available to an individual or group of assessors based on education, experience, and reason	May rely too much on what seems important as opposed to what should be considered (becomes less of a concern with training and experience)

Similarly, an organism with a narrow geographic range would be of less concern than one with a wide or unknown range.

Familiarity Approach

This popular line of approach advances the concept of relative risk assessment. The determination of level of concern is based not only on the genetic characteristics of the organism, its phenotype, and the environment into which it will be released, but also on a comparison of the GM organism to the corresponding well-known non-GM organism, and the GM trait derived from classical genetic techniques. In other words, how "familiar" scientists are with a particular organism and trait helps them to determine the appropriate level of concern. The essence of the argument is that because most crop plants are genetically modified in increments, the amount of new genetic material is a very small percentage of the plant's genome, and, regardless of how the trait was derived (through classical breeding or by modern molecular techniques), it will phenotypically be the same. For example, by comparing GM plants with the parental plants that, based on past introductions, have a safe history, it is possible to arrive at a reasonable assessment of how the modified plants will behave in the environment.

Formulaic Approach

Some regulatory agencies have modified the basic risk-assessment approach used for chemicals to use with biotechnology products. In essence, categorical considerations of hazard (H) ascribable to a chemical and the chemical's potential exposure (E) to individuals or groups of individuals are determined. In combination, they determine a level of risk (R). This is commonly described algorithmically as $R = H \times E$. The important insight this equation offers is its inherent organizational nature. The analysis may be subdivided into manageable parts. Using estimates of a potential impact (hazard) and the proximity of a material to the potentially affected component of the environment (exposure), an estimate of the level of risk is obtained. Both hazard and exposure are necessary for risk to be present. That is, presence of a hazard without exposure, or exposure to something that is not hazardous, poses no risk. Other considerations such as dose response (a measure of the level of potential impact) and risk characterization (severity of concern and level of uncertainty) complete the process. More recent thinking about this paradigm has led to minor alterations in the basic formula to recognize and account for the nature of organisms as opposed to chemicals. These alterations include the addition of terms for survivability (fitness), mutation, and reproduction.

Intuitive Reasoning

Assessors tend strongly to rely on their intuition when evaluating applications to release GMOs. Of course they are educated and have considerable expertise, usually in a specific discipline, but because they will have to make decisions with incomplete information, they tend to base decisions on what "feels right." Unlike the previous approaches, the intuitive approach has no structure per se on which to develop an assessment; individual assessors have differing intuitions. Because some measure of consistency is lacking, risk assessors using only this approach may find it more difficult to communicate with other assessors and decision makers.

Despite the inherent level of uncertainty involved in a risk-assessment process and the fact that, at present, assessors are addressing events with a low probability of occurring, using a systematic approach to risk assessment is a worthwhile exercise. When used appropriately, the approaches described above will help to organize scientific information, facilitate communication, and minimize paralysis in decision making.

Practical Considerations

Risk Assessment is Subjective

Although risk assessment ideally should be objective and unbiased, the process is necessarily affected by the unavoidable biases and limitations of individual reviewers – their education, work experience, social values, and cultural background. External factors such as policy decisions at local, regional, or national levels, and public perceptions and attitudes likewise color the context for biosafety committee deliberations. These factors will affect reviewers' comprehension, analysis, and judgment.

Objective biosafety assessments should be based on the best science available. (As we discussed earlier, *decision making* on the use of GMOs also takes into account various nonsafety factors such as economic impact, dietary and nutritional needs, religious and social values, and the like.) In reality, however, other influences will creep into the assessment process. For example, national policy determinations on the institutional home of biosafety and type of regulatory instrument employed (e.g., regulations under the ministry of environment vs. biosafety legislation in the ministry of agriculture) will shape assessment objectives and the configuration of review panels. Figure 1 (page 8) suggests a balanced influence of these factors on risk assessment, but this is rarely obtained in practice. It is much more likely that one or two of these factors will dominate the decisions that will be made.

This is certainly so when dealing with biological materials and their potential interactions in the environment. The number of possible permutations and combinations will easily challenge the most talented assessor. Whether risk assessment methodology is considered a "scientific activity" or an "analytical tool," understanding and using it may be the only acceptable means for making determinations for the safe development and use of biotechnology products.

Imperfect Knowledge

Findings based on scientific data are often limited by incomplete or missing information. It is not uncommon for biosafety committees to raise questions for which experimental data are lacking. Their deliberations must accommodate this inherent limitation of risk assessment. Otherwise, a circular argument results: if all questions must be answered before approving a field test, and if the answers can be found only by conducting field tests, then no approvals can be granted. Part of the solution to this difficulty is to actively seek all available information (beyond that provided in the application), weigh the history of use and collective experience of experts, and use this to recommend appropriate management controls (see section four, "Risk Management") as a condition for approval.

Scale-up

The risk assessor needs to be aware of the spatial and temporal scale of GMO introductions. Questions may change as the size of the area being planted changes. For example, some questions pertaining to commercial-scale release cannot be answered by data from small-scale field tests (e.g., probability of gene transfer). Low-probability events are more likely to occur when large numbers of plants are cultivated. Differences in scale may have profound effects on the ability to provide meaningful monitoring when called for, or to devise reasonable and affordable methods to monitor specific events of concern (see section five, "Monitoring"). Fortunately, the normal progression of genetically modified crop plants allows for the accumulation of useful information as the GM product progresses from the laboratory to the market.

Benefits of Iterative Processing

The iterative — regularly repeated — nature of risk assessment is fundamental to good assessment practice (Figure 2, page 28). The question-and-answer "conversations" inform applicants of regulatory concerns so that they may provide additional information, satisfy unintended omissions, and clarify language. Information gaps that become evident through the process draw attention to biosafety-related topics that need to be researched.

Reviewers interact primarily with applicants during the review process. Contacts with the scientific community, decision makers, and the public may be likely as well. By conducting several rounds

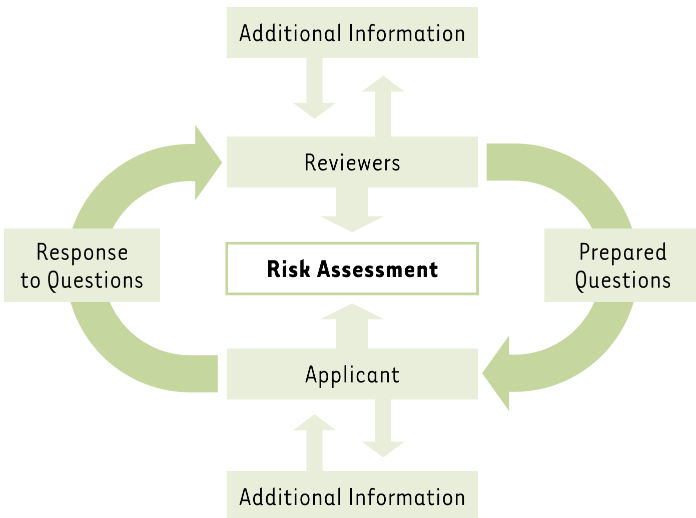


Figure 2. The iterative nature of risk assessment. Risk assessment proceeds by cycles of questions and answers between the applicant and biosafety reviewers. Through this interactive process, initial and emerging information needs can be addressed so that the biosafety committee can formulate a set of recommendations regarding the proposed activity.

of questions and answers with the applicant, reviewers have an opportunity to ask new questions based on points raised by outside contacts, thus bringing wider input to the risk-assessment process.

Use of Expert Committees

Although not always required, expert committees offer an invaluable adjunct to risk assessors. They not only expand the pool of expertise brought to bear on specific issues, but also provide stimulating debate around the limitations of scientific data to arrive at conclusions and the uncertainties that must be considered. These advisory groups have been used successfully for many years.

Already limited in the supply of national experts, developing countries with active biotechnology research programs may be particularly hard pressed to find independent reviewers/assessors without a conflict of interest. This gap may be partially filled through regional cooperation or the use of expertise from the larger international community. The costs of assembling such experts must be taken into consideration. Alternatively, making experience and information available in written form may help to fill the void. In a practical sense, however, providing useful, relevant information is not a trivial task and, in fact, may be limited.

Scientific Issues for Environmental Risk Assessment

Concerns about the impact that GMOs may have on the environment center around their potential to displace or "genetically contaminate" native species and their potential to cause deleterious effects on other organisms. Either consequence could disturb existing ecological relationships or in some unintended way change the living (biotic) or nonliving (abiotic) components of the surrounding ecosystem. Of primary concern is the potential threat to the biodiversity of organisms living in and around a commercial release site.

The negative environmental impacts associated with agricultural biotechnology products can be generally grouped into four areas: weediness, gene flow, pest or pathogen effects, and toxicity to other organisms. Food-safety evaluations address a very different set of potential concerns and typically are handled through a different government agency. (A brief treatment of the subject may be found in "Human Health and Food Safety" on page 33.) Because of the differences between field tests and commercial releases in terms of scale, physical control, management options, and other parameters, risk issues are viewed somewhat differently for the two types of release.

Weediness

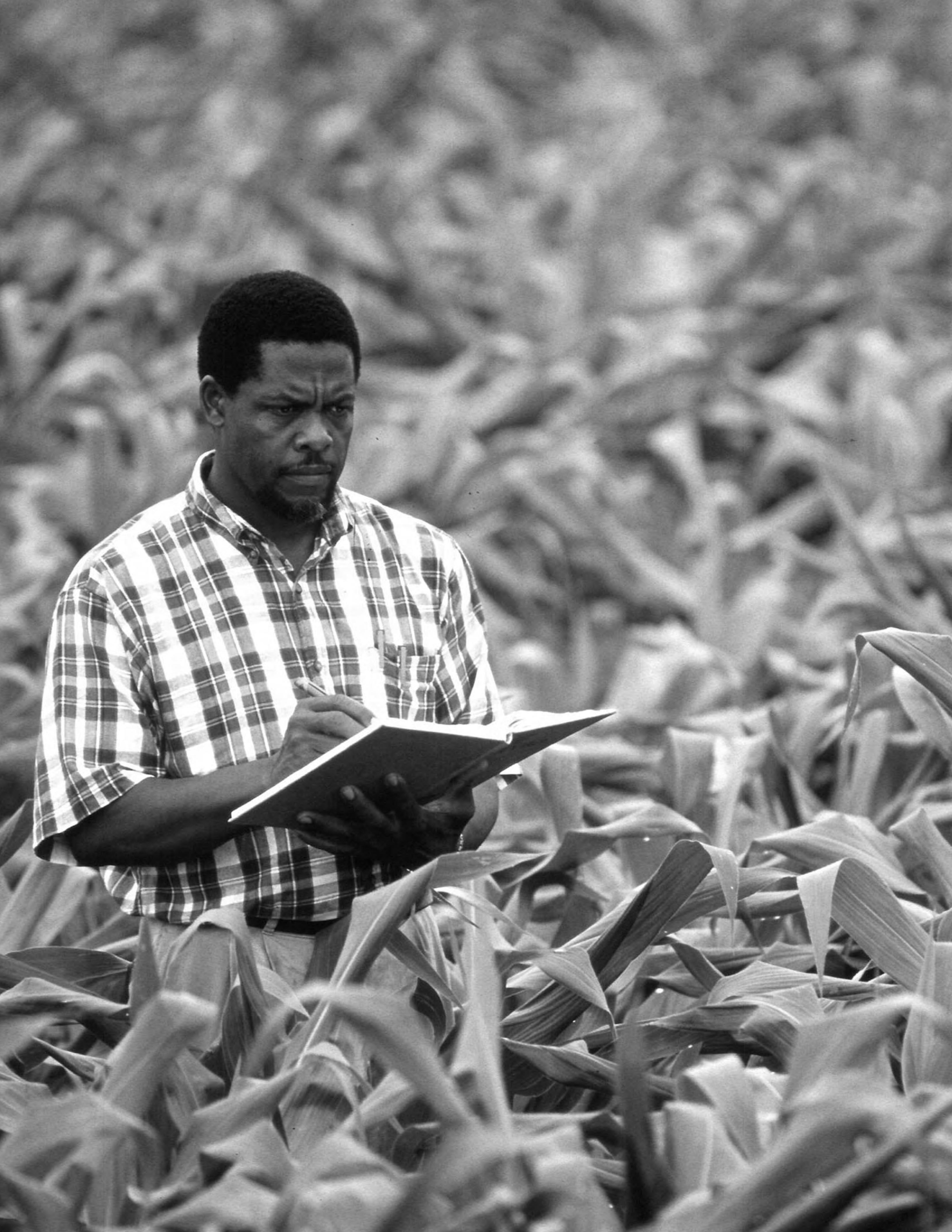
The concept of weediness—with its numerous characteristics contributing to complex and variable phenotypes—is difficult to define. Weediness is not an inherent property of certain plant species, but rather is a judgment based on the time and circumstances in which the plant is growing in light of human preferences at that time and place. Thus the simplistic definition of a weed is "a plant in a place where you don't want it." In cultivated fields, a GM crop may become an agricultural pest (weed) by showing up as a "volunteer" in subsequent planting seasons. If engineered for tolerance to a particular herbicide, the "weeds" would be more difficult to control, requiring application of a different herbicide or use of alternative weed control measures. True weediness, however, results from the action of many, many genes. Most crop varieties have been domesticated sufficiently to be nearly incapable of surviving outside of managed agricultural fields; it is unlikely that any single gene transfer would enable them to become pernicious weeds.

Some single-gene traits introduced by genetic engineering may confer a weed-like characteristic that enhances fitness. For example, if a crop's ability to grow in areas outside a cultivated field is held in check by a single limiting factor such as a fungal disease, engineering resistance to the fungus may give the crop an increased ability to spread into adjacent areas. Thus the GM crop, no longer susceptible to the limiting factor, may gain a selective advantage in the local environment by exhibiting the weed-like behavior of invasiveness. Therefore, it may threaten to displace native species. This presents an environmental concern if (and only if) the crop has sufficient genetic capacity to become established and persist in those new unmanaged areas.

Of greater concern is the potential for less domesticated self-seeding crops (alfalfa) and commercial tree varieties (pine, poplar, eucalyptus) to become problems. These plants already have a capacity to survive on their own; transgenes could enhance their fitness in the wild. Pine trees, for example, engineered for resistance to seed-feeding insects might gain a significant advantage through decreased seed destruction, potentially allowing them to out compete other indigenous species. If that happened, forest communities could be disrupted.

Gene Flow

The possibility that genes introduced by genetic engineering may "escape" (be transferred via pollen) to wild or weedy related species growing nearby is often cited as one of the major risks of GMOs. Gene flow between crops and the wild species from which they were derived, however, is a well-documented natural phenomenon. Over the course of evolution, familiar crop species – wheat, potatoes, corn, canola, and numerous others – were modified from their original form because of hybridization with related species or weedy or culti-



vated strains growing nearby. Through this long-established mechanism for gene transfer, any gene in a cultivated crop or plant, irrespective of how it got there, can be transferred to its wild or semi-domesticated relatives.

The real concern is *not* that such outcrossing will occur—because we know that it does—but rather that negative consequences may result from it. In some cases, serious weeds are relatives to crops (Johnson grass to sorghum, wild mustards to canola, red rice to rice). If a wild plant's fitness is enhanced by a transgene that gave it protection from naturally occurring pests or diseases, would the plant become a worse pest (the "superweed" scenario), or would it shift the ecological balance in a natural plant community? Wild relatives of crops suffer from disease and insect attack, but few studies address whether resistance to pests in wild plants would result in significant ecological problems. Weeds often evolve resistance to disease by natural evolutionary processes. However, in some cases, gene transfer from crops could speed up this process considerably.

Wild races are especially important weeds in direct-seeded rice fields, which are becoming more common in Asia. It has been shown that genes often are naturally transferred between domestic rice and weedy wild races. In commercial fields planted to a genetically engineered herbicide-tolerant (HT) rice cultivar, weedy wild rice could be controlled by applying the herbicide, *until* the wild rice acquired the HT gene from the cultivar. At that point, the herbicide would become useless. In this case, the wild rice would not become a worse weed as a result of acquiring the HT gene. It would simply be more difficult to control and would nullify the benefit of the engineering effort. Weeds can evolve resistance to some herbicides without gene transfer, but the process takes much longer. For example, herbicides such as glyphosate (RoundUp™) from Monsanto are difficult for plants to resist with their normally inherited genes. Nonetheless, in Australia decades of intensive use of glyphosate have led to the emergence of resistance in some weed populations.

Two other gene flow concerns deserve mention. First, nontransgenic crop plants may be pollinated by a GM variety growing in an adjacent field. If the GMO is engineered to produce a protein harmful to certain organisms, the protein may be present in the seed and progeny of the non-GMO plants. Conceivably, the gene transfer may escape the notice of those growing the non-GM variety and other organisms may unknowingly be exposed to the harmful protein. Second, gene transfer to diverse organisms (microbes, animals) is not impossible, but the probability of such an event is exceedingly low. It is not normally a major factor in biosafety reviews.

Pest or Pathogen Effects

A GMO may worsen an existing pest or pathogen problem in a variety of ways. Currently the most common genetic engineering approach to increase plant resistance to insect pests is the "Bt strategy." This is based on the discovery that strains of a soil-dwelling bacterium, *Bacillus thuringiensis* (Bt), produce a class of proteins selectively toxic to many insect species that attack crops. Farmers and gardeners have used microbial sprays of Bt for many years to control insect pests as part of integrated pest-management programs. Bt insect control proteins have been engineered into major commodity crops and a growing list of vegetable, fruit, and tree species. The potential consequences of extensive and long-term use of Bt crops are one of the most widely discussed environmental issues associated with transgenic crops. The concern is that as insect pest populations increasingly are exposed to high levels of Bt proteins over long periods, emergence of resistant individuals within the pest population will be accelerated. This concern with pest resistance to transgenic pesticides is the same as that with resistance to chemical pesticides as a result of overexposure. Many experts agree that the question of pest resistance to Bt is not "if" but "when." This is particularly important in organic farming where chemical alternatives are not acceptable.

The *de novo* generation of new viruses from virus-resistant (VR) engineered crops has also been raised as a potential risk. To date, the most widely used biotechnology approach to controlling plant virus diseases has been the use of genes derived from the plant viruses themselves. For a number of important virus pathogens, expression of the viral coat protein gene in the host plant inhibits replication of that virus. In addition to being the structural component of virus particles, coat proteins also play a role in determining the host range of the virus and serve other functions as well. For some virus groups, other viral genes have been used successfully to limit disease.

The presence of viral sequences in major crop plants may increase the likelihood of creating novel viruses through molecular recombination between the transgenes and the genomes of other viruses that infect the plant. Such exchange of genetic information encoding coat proteins genes, for instance, could lead to the production of a new recombinant virus that has a unique coat protein that alters its host range. Similarly, recombination between other transgenes and infecting viruses could yield new virus strains with novel characteristics. Multiple plant viruses simultaneously infect many crops, and there is strong molecular evidence that virus evolution has proceeded rapidly through the exchange of large blocks of genetic information via recombination. Ongoing studies are examining the frequency of recombination events in naturally infected plants compared with transgenic VR plants.

Toxicity

There are some concerns regarding the safety of new proteins expressed in transgenic plants. Even low-level expression of a new transgene potentially may have an unintended, deleterious effect on other organisms including birds, insects, browsing animals, and soil organisms in the local environment. This is particularly the case when the protein has no prior history of being found in plants, or is not found at the levels expected in the GMO.

Proteins intended to control specifically targeted pests may be harmful to nontarget species. In terms of plant-produced insecticides, the only insecticidal compounds that currently are commercialized are the toxin proteins naturally produced by Bt. These proteins are highly specific in their toxic effects. One group of these proteins affects only certain species of caterpillars whereas others affect only a restricted set of beetles. None of these proteins has been shown to have a significant disruptive effect on predators of pest species or beneficial insects.

The toxicity issue (and any potential risk issue) can sometimes be inflated to alarming proportions. A report that pollen from Bt corn killed larvae of the monarch butterfly was taken to mean that Bt crops were harmful, prompting extensive negative press coverage. Numerous studies seeking to verify and clarify the reported findings all found that, under field conditions, monarch populations were not harmed. This episode may serve to underscore to biosafety reviewers the importance of carefully examining the quality and credibility of data relevant to biosafety decision making.

Risk-Assessment Research

Biosafety reviewers often face uncertainty when certain data needed for a complete evaluation are missing. Risk-assessment research is designed to provide information and generate data that fill in knowledge gaps and expand basic understanding of crop biology, agricultural ecosystems, and the ecological interactions of crop plants and their environment.

High-priority topics for risk-assessment research are often identified in the course of biosafety reviews. They may take the form of questions such as:

- What characteristics of the crop limit its ability to become established, persist, or spread in the environment where it grows?
- How will the genetic modification change this?
- In cases where crops and their wild relatives are known to hybridize naturally:
  - Are there genetic mechanisms that favor or hinder gene introgression?
  - What is the relative fitness of hybrid progeny?
  - Will they have ecological characteristics that are more problematic than either parent?
- Where the engineered trait confers pest resistance:
  - What are the potential secondary effects? (e.g., changes in local/field-level ecology)
  - What new problems may develop as a result? (e.g., emergence of alternative pests as a consequence of changes in pesticide applications)
- Where the engineered trait confers virus resistance:
  - What viruses other than the target virus infect the crop?
  - What is the incidence of multiple virus infection?
  - What are the similarities and differences in the replication mechanisms of infecting viruses?
- Regarding the new gene product:
  - What parts of the engineered plant will contain the new protein?
  - What nontarget species will be exposed to it?
  - What is its toxicity to those species?
  - What is their expected level of exposure?
  - What are the likely biological effects of exposure?

These questions, and others like them, reflect sharpened awareness of (1) the ecological complexities of cultivated fields and adjacent areas; (2) the potential for long-term effects whose nature and probability can only be guessed; and (3) the knowledge gaps that hamper science-based decision making. These same types of questions, modified to fit a particular interaction among crop, introduced trait, location, and scale and expanded to cover any other applicable environmental or ecological considerations, constitute the basis of risk assessment for a proposed GMO field test or commercial use. It must be emphasized, however, that *lack of complete knowledge should not prevent biosafety decision making. An element of uncertainty will always be present.*

Human Health and Food Safety

The primary human health concern with foods produced from transgenic crops is that new proteins expressed in the GM plant may be hazardous – they may be toxic or cause an allergic reaction. Other hazards may include reduced levels of certain nutrients, or elevated levels of certain antinutrients. Genes themselves are made of DNA and are present in all foods. DNA ingestion is not associated with any negative health effects.

In general, health ministries are responsible for the safety of foods including those derived through biotechnology. Biosafety risk assessors review data on the nature and expression of newly inserted genes, detailed characterization of new proteins, changes in composition or nutritional qualities of food, intended new uses of the product, and a comparison of the new food with conventional counterparts.

Countries that are signatories to Codex Alimentarius, the international commission that sets food safety standards, usually have reactive rather than proactive food-safety regulations in place – that is, regulatory supervision begins only when products are commercialized. Codex requires that any new food that varies from its conventional counterpart in composition, nutrition, or intended use must be labeled as such. Thus, according to Codex rules, foods produced using oil from GM canola having a modified fatty acid profile are routinely labeled. Note that labeling is required because of the altered composition of the oil, not because it came from a GM crop.

Assessing Food Safety

Many plants routinely used for food contain toxins (e.g., beans contain lectins, potatoes contain alkaloids). Any method of crop improvement (by traditional breeding practices or through biotechnology), can possibly introduce unknown changes in food composition. New varieties that contain an increased amount of toxic compounds may be hazardous. This is one reason why countries with crop variety registration procedures usually look at certain aspects of food safety before registration of new, conventionally derived varieties.

The first step in a food-safety review is testing of the new protein expressed from the inserted gene. If the protein is not already present in other foods with a proven history of safety to humans, it is thoroughly tested to ensure its safety. Even if the newly expressed protein is well known, studies are conducted with the GM material to confirm its safety and to assess whether any unexpected effects occur in the plant.

Genetic engineering need not make a food inherently different from its conventional counterpart. The technology itself is unlikely to increase the food's probability of containing an allergen. Concern about food allergies, however, is frequently cited as a major consumer issue with GM foods. Fortunately, much is known about foods that trigger allergic reactions—for example, 90% of all food allergies in the United States are caused by a very small number of foods: cow's milk, eggs, fish and shellfish, tree nuts, wheat, peanuts, and legumes.

The amino acid sequence of the new protein is compared to that of known allergens. A very high dose of the expressed protein is fed to laboratory animals to assess toxicity, and immunological tests are conducted to ensure that the newly expressed protein is not an allergen. Digestibility studies are carried out with the purified protein and with the whole food. These tests determine whether the new protein is rapidly digested like other dietary proteins (a trait generally indicating nonallergenicity). If digestion breakdown products result, they are identified and checked for safety.

(Initially there was some concern that virus proteins expressed in virus-resistant GM crops might trigger allergic reactions if included in food. This concern has largely been abandoned since many foods are infected with one or more plant viruses, and viral proteins have been consumed thousands of years without deleterious effects.)

Even genes from sources not known to be allergenic are subjected to detailed allergenicity screens. The level of the new protein in the GM plant and the amount present in parts consumed as food are assessed to estimate how much would be consumed in a normal diet. Studies on whole foods indicate whether the inserted genes or new protein might have an unexpected effect on the normal composition and qualities of the food. Tests are performed to determine whether nutrients, vitamins, and minerals in the new plant occur at the same level as in the conventionally bred plant. Other studies examine whether antinutrients (substances that interfere with nutrient absorption), natural toxicants, or known allergens occur at levels comparable to those in the conventional plant. In some cases, baseline data on conventional foods against which comparisons with GM foods can be made are lacking.

When foods derived from transgenic crops and their conventional counterparts are demonstrated to be essentially the same, the GM food is said to be "as safe as" or "substantially equivalent to" the conventional product. Any significant change in nutrition, composition, or intended use prevents the claim of substantial equivalence. While the first generation of transgenic crops largely fulfils the substantial equivalence requirements, subsequent generations will include many types of food GMOs specifically designed to be nutritionally enhanced and therefore different. For these, substantial equivalence will not be an appropriate measure of safety.

Collection of Food Safety Data

Gathering food- and feed-safety data is an expensive process. For this reason, developers collect data according to the stage of product development. During the laboratory research stage, if the inserted gene(s) comes from a source known to contain allergens and the GMO under development is intended for the food or feed industry, it is prudent for developers to check the introduced proteins for allergenicity or toxicity. Preliminary food-safety checks usually involve comparisons of the cloned gene with the DNA and amino acid sequences of known allergens and toxins and, if indicated, the protein may be subject to clinical testing. If the protein is found to be potentially allergenic or to have unacceptable toxic properties, further development of the GMO may voluntarily be halted. Otherwise, good laboratory practice simply requires that experimental GMOs be neither eaten nor allowed to enter any food chain.

As GM lines advance to greenhouse trials, good reason seldom exists to require collection or submission of food- and feed-safety data for approval from the biosafety committee, except when it is difficult to exclude the possibility that the GMO will enter the food chain. Greenhouse studies are used primarily to test for efficacy of the introduced trait and to identify individual lines that will be further tested in field trials. For lines showing promise, however, developers may use greenhouse trials to begin collecting data that later will support a commercial-use application. Greenhouse experimentation can provide the material needed for initial testing of, for example, levels of the foreign protein found in various tissues and at various stages of growth.

Field trials give the first clear indication of how GMOs perform in the environment. At this point, it is usually prudent to make a preliminary assessment of food and feed safety. If data on the GMO's potential toxicity and allergenicity are not complete, regulators typically will require that field trials be conducted at sites not accessible to the general public and that measures be taken to insure against accidental release of GM material into local food chains. Means to control access to the trial site, including access by unauthorized people, animals that may feed on the GMO, and other organisms likely present in the field test area are carefully evaluated by risk-assessment reviewers.

Once individual lines ("events") have been chosen for commercialization, collection of relevant food-safety data begins in earnest. Material from field trials is gathered and used in comparative assessments against the non-GM variety. Food- and feed-safety reviews generally focus on the products of the foreign genes and the characteristics of the whole food. Investigations consider:

- Toxicity to humans, other animals, birds, fish, insects, and soil microbes[6]
- Pathogenicity
- Allergenicity
- Nutritional and compositional changes
- Digestibility and digestion products
- Stability of gene products and the genes in the food source
- The fate of genes and gene products in food processing
- Any other area that food technologists believe is important to evaluating the safety of the new food for humans and animals

To date, all proteins introduced into transgenic crops currently approved for human consumption have been shown to be nontoxic and nonallergenic.

Marker Genes

As part of the genetic modification process, "marker" genes are usually linked to the gene of interest to make it easier to determine whether the treated cells or tissues are in fact genetically modified. There is some concern that the use of antibiotic-resistance genes as markers in transgenic crops might cause or increase resistance to antibiotics in microorganisms that cause disease in humans and animals. In other words, could use of these genes increase the problem of drug-resistant "super bugs"? Antibiotic resistance is a serious public health issue. However, scientists widely agree that the root cause of the problem is the overuse or misuse of antibiotics in clinical treatments and animal production. As such, the possibility that use of antibiotic-resistance marker genes in crops could pose a public health concern has been largely discounted.[7] Nevertheless, food developers have started to pursue alternative types of marker genes, and in time it is likely that antibiotic-resistance genes will no longer be used. New marker genes and their products will be subject to the same rigorous biosafety assessment.

These assessments allow regulators to conclude whether a biotechnology product attains a common safety standard expressed as "reasonable certainty that no harm will result from intended uses under the anticipated conditions of consumption." If the GM crop or inserted DNA does not cause a change in any of the numerous parameters examined, regulators are able to conclude with confidence that the food is safe for consumption.

4 Risk Management

Risk management in the context of agricultural biotechnology is the use or application of procedures and means to reduce the negative consequences of a risk to an acceptable level. Attention generally is focused on limiting risk by proper handling and use of various preventive measures. In fact, opportunities to manage potential or identified risks can be found throughout the process of developing and testing genetically engineered organisms.

Risk Management in the Laboratory and Greenhouse

GMO Design

When planning a genetic engineering project, scientists work out the molecular details of the GMO they intend to produce. These details include identification of DNA sequences encoding the desired trait, choice of marker genes, and nature of regulatory sequences that will direct expression of the transgene. Choices are also made regarding minimization of extraneous DNA, options for targeting the site of insertion, as well as the method of transformation.

Transformation methods for inserting new genes into plants are relatively inefficient; only a very small proportion of treated cells actually take up the new DNA. Marker genes are included in the segment of inserted DNA in order to distinguish cells that contain the new genes from those that do not. Some marker genes encode enzymes that lead to the production of a pigment or fluorescent light, allowing easy identification of GM cells. Other marker genes encode proteins that inactivate antibiotic compounds; when treated cells are grown in the presence of the antibiotic, only those that took up the new DNA are able to survive. In the past, the gene encoding neomycin phosphotransferase II (*nptII*, the so-called "kanamycin gene") was the preferred marker because it provided a cheap and effective way to grow selectively only the GM cells.

Concern arose that GM plants containing antibiotic-resistance genes would, if consumed as food, present a risk to individuals taking the antibiotic as a therapeutic agent. Despite numerous detailed studies that unanimously concluded the risk was immeasurably low, and despite approval by the food safety regulatory agencies in numerous countries, public opinion remains opposed to the presence of antibiotic-resistance marker genes in foods. In response, developers of GMOs to be used as food are moving away from these genes. Ongoing efforts are under way to identify other types of genes useful as markers and to develop methods for removing marker genes before GM products get to the market. It is worth noting that even though the protein encoded by the *nptII* gene presents negligible biosafety risk, GMO designers are well advised to consider such concerns.

Molecular biologists have identified a number of promoters able to turn on gene expression in specific tissues. In plants, these tissue-specific promoters restrict transgene expression to roots, leaves, or other selected tissues where the new protein is desired. For example, a leaf-specific promoter, directing toxin production in the leaves but not roots, stems, or flowers, could control a gene encoding a toxin active against a leaf-attacking pest. In transgenic animals, a tissue-specific promoter has been used to direct transgene expression in mammary glands so that the new protein is secreted in milk.

Inducible promoters can switch transgene expression on and off during the life of the plant. For example, certain promoters respond to a chemical signal; simply spraying the transgenic plant or plant part with that chemical can activate them. Water stress, temperature, mechanical damage, light, or various other types of stimuli activate other inducible promoters. The next generation of GMOs is expected to make use of these more sophisticated gene regulatory sequences that can contribute to reducing potential risks.

Cells transformed by *Agrobacterium*-mediated DNA transfer methods usually contain, in addition to the desired gene or genes, extra pieces of DNA that come from the *Agrobacterium* vector. Although vector-derived sequences rarely cause any problem, one view holds that the safest approach to designing GMOs is to avoid including any extraneous DNA sequences. An alternative approach, direct gene transfer via a "gene gun" or electroporation, avoids the potential for inserting unnecessary vector DNA because no vector is used. Other transformation methods make it possible to insert transgenes into chloroplast DNA. The value of this approach is that pollen grains of most, but not all, plant species do not contain chloroplasts; therefore, concern about the spread of transgenes via pollen (gene flow) is essentially eliminated.

Although these methods of advance risk management are easy to implement, they must be integrated into the research plan before the first candidate GMOs are produced. If applied, they simplify later risk assessment by avoiding certain features known to raise questions of risk.

Containment

As a GMO under development progresses through the laboratory to the growth room and into the greenhouse, the basic biosafety requirement is to limit spread of the engineered organism and its genetic material. *Containment* is a term for the use of physical barriers to restrict spread within a structure or enclosed space. Laboratory facilities and greenhouses afford this relatively high level of control.

Laboratory containment

Physical containment of transgenic plants and plant cells within laboratories, tissue culture facilities, and growth cabinets is maintained by good laboratory practice. Plants can be monitored relatively easily under such conditions, although care must be taken to ensure that seeds produced under lab or growth cabinet conditions are carefully collected for disposal or subsequent use. Labeling plants or pots will help avoid accidental mixing of transgenic and nontransgenic plants. Materials to be disposed of need to be treated in a way that prevents their survival or growth outside the contained facility. This may be achieved by autoclaving, steam sterilization, treatment with a household bleach solution, or proper composting.

Greenhouse containment

Greenhouses are designed to keep insects and animals out and plant and plant parts in. Construction details and procedures for handling GMOs will vary depending on the types and degrees of biosafety concern associated with the experimental materials to be housed within. In many cases, conventional greenhouses can be made suitable for GMOs by simple refurbishing and minor structural upgrades. For higher levels of containment, facilities may have to meet such specifications as controlled and filtered airflow, systems to control and disinfect water leaving the facility, autoclaves for on-site sterilization of plant material and equipment, disinfecting the facility after experiments, strict limits on whom is allowed to enter, and staff and worker training. Consideration also must be given to safe transport of GMOs into and out of the facility and methods to monitor for accidental escape during and after the experiment.

Greenhouses cannot prevent pollen from escaping; even newly built, top-quality greenhouses will not contain microscopically small grains of pollen. Pollen containment requires specialized equipment, materials, and expensive construction details that may be beyond the means of most public institutions. An easy and commonly used solution to this problem is to place small bags over the male flowers before the pollen is shed; collected pollen may then be used for hand-pollination as needed, or disposed of. More effective containment is achieved by building within the greenhouse a small sealed room fitted with special air filters that block pollen escape. For more detailed information, refer to *A Practical Guide to Containment: Greenhouse Research with Transgenic Plants and Microbes*.[8]

Risk Management in the Field

Environmental risk is a function of the combined characteristics of the organism, the nature of the genetic modification, and the site (local ecosystem) where the GMO is to be released. Each characteristic affords opportunities to manage potential risks. Not all GMOs pose an environmental risk; of those that may cause harmful effects, not all pose the same level of risk. Accordingly, biosafety reviewers strive to tailor risk-management procedures to the nature and magnitude of an identified risk. Some of these strategies are discussed in the following sections.

Confinement

Confinement, or measures to keep experimental organisms within a zone having designated borders or limits, is the most common method for preventing or minimizing the unintentional spread of a GMO or its genetic material.

Physical strategies for confinement

Physical means to confine GM plants and plant parts include geographical or spatial isolation or use of structures such as fences, screens, mesh, and the like to keep animals out and prevent "unauthorized harvest." In order to be considered an environmental risk, transgenic pollen must be able to fertilize plants of a sexually compatible

Isolation Distances (in meters) from Contaminating Sources for Selected Crops

Crop	Foundation	Registered	Certified
Corn (inbred)[a]	200	—	—
Corn (hybrid)	—	—	200
Cotton (hybrid)[b]	0	0	0
Millet (selfed)[c]	400	400	200
Millet (crossed)[d]	0	0	0
Mung beans[d]	0	0	0
Onion	1,600	800	400
Peanuts[d]	0	0	0
Pepper	200	100	30
Potato (male fertile)	400	400	400
Potato (male sterile)	0	0	0
Rapeseed (selfed)	400	—	100
Rapeseed (crossed)	200	—	100
Rice	3	3	3
Sorghum (hybrid)	300	300	200
Sorghum (hybrid)	—	—	200
Soybeans[d]	0	0	0
Sunflower[e]	800	800	800
Tomato	200	100	10
Watermelon[f]	800	800	400

SOURCE: Modified from "Genetic and Crop Standards" of the AOSCA: *http://www.aosca.org/*

a. No isolation is required for the production of hand-pollinated seed.
b. Isolation distance between upland and Egyptian types must be at least 400, 400, and 200 meters for Foundation, Registered, and Certified classes, respectively.
c. Distance adequate to prevent mechanical mixture is necessary.
d. Isolation between millets of different genera must be 2 meters.
e. An isolation distance of 1,600 meters is required between oil and nonoil sunflower types and between either type and other volunteers or wild types.
f. The minimum distance may be reduced by 50 percent if natural or artificial barriers adequately protect the field.

species growing in the vicinity. Crop breeders are an excellent source of information about the presence and distribution of cross-fertile wild or weedy relatives of cultivated species. *Genetic and Crop Standards*, an annual publication of the Association of Official Seed Certifying Agencies (AOSCA[9]), describes the isolation distances required to avoid genetic contamination by pollen dispersal in the production of certified seed. (The terms *foundation, registered*, and *certified* refer to classes of certified seed produced and handled under procedures established by the certifying agency according to each class for maintaining genetic purity and identity. In simple terms, they are the first-, second-, and third-generation progeny of breeder seed, respectively.) The accompanying table shows isolation distances for the three certified seed classes of selected crops.

Where available land is insufficient for spatial isolation, one or more of the following procedures can reduce or prevent GMO or transgene spread via pollen or seed:

- Plant border rows of the non-GM variety around the test plot to "trap" pollen from the GMO.
- Bag flowering structures to screen out pollinating insects and/or prevent pollen spread by insect vectors, wind, or mechanical transfer.
- Cover female flowers after pollination to prevent loss or dissemination of GM seed.
- In cases where research objectives do not require seed production for analysis or subsequent planting, remove flower heads before pollen and seed production.
- Harvest plant material of experimental interest before sexual maturity.
- Locate test plots surrounded by roads or buildings.

Biological strategies for confinement

Biological processes can provide highly effective means of preventing unintended transmission of genetic material. Reproductive isolation, a common method of biological confinement, can be achieved in a variety of ways:

- Grow GM plants in an area where sexually compatible wild or weedy species are not found.
- Remove all plants of sexually compatible wild or weedy species found within the known effective pollinating distance of the GM crop.
- Cover or bag flowers to screen out insect pollinators or prevent wind pollination.
- Prevent production of viable pollen by using genetic male sterility, applying a gametocyte, or removing all reproductive structures at an early stage of development.
- Recover tubers, rhizomes, storage roots, and all tissues capable of developing into mature plants under natural conditions.
- Exploit differences in flowering time so that GM pollen is not shed at the time when sexually compatible plants nearby are receptive.
- Engineer genes into chloroplast DNA instead of chromosomal DNA, since pollen from most species does not contain chloroplasts. This technology is still in its infancy, may not be effective for all genes, and would not be effective in plants in which chloroplasts are transferred by pollen.
- Engineer transgenic plants to produce sterile seed. This technology was developed as a "technology protection" system to secure intellectual property rights for the improved seed (the so-called Terminator gene). It is highly effective for risk- management purposes, but has raised ethical questions regarding seed saving and the role of multinational corporations in controlling seed and therefore food supplies in developing countries.

Other strategies for confinement

For small-scale field tests, environmental conditions can be manipulated to limit reproduction, survival, or dissemination of GMOs outside the experimental area. For example, temperature, water supply, humidity, and photoperiod can be controlled naturally by suitable placement of the test site, or artificially by using irrigation, lights, misters, and the like. In some parts of the world, trials can be conducted in which climatic conditions preclude flowering or survival outside the experimental area.

Chemicals can be used to limit survival and reproduction of GMOs outside the trial area. Herbicides, fungicides, insecticides, disinfectants, or other materials toxic to the test organism can be applied, but effects of the chemical on other organisms or the immediate vicinity must be taken into account. At the end of an experiment, the whole experimental area, if necessary, can be treated chemically or sterilized. Lastly, decreasing the number of test organisms or the land area used in an experiment may reduce the possibility of unintended dissemination.

In sum, organisms that engender little or no risk to the environment may require no or minimal confinement. GMOs with a very high potential for causing serious adverse effects *in some cases* may not be safely grown outside of containment. Most agricultural GMOs will be found safe for small-scale (field-test) release when specific risk-management procedures are part of the experimental design.

Other Standard Risk-Management Procedures

Termination and Follow-up Procedures

Measures are usually implemented at the end of laboratory, greenhouse, and field trials to ensure that the GMOs are effectively removed from the experimental area. The required measures are determined by the type of organisms, their natural means of spread, and the environment in which testing was carried out. As such, the requirements for cleanup must be determined on a case-by-case basis.

For microorganisms, some form of disinfecting may be necessary. For plants, harvesting seed and ploughing in or burning residual plant material are usually effective where vegetative reproduction does not occur. This is followed by a fallow period during which volunteer plants arising from escaped seed or from vegetative reproductive structures are monitored and destroyed before the onset of flowering. The extent of the fallow period is dependent on the climate and crop. Cold winters are effective seed and tuber destroyers for many crops. Harvested seed and plant material must be documented and stored, or disposed of, according to the requirements of the regulators. This, too, is crop dependent.

Record Keeping and Reporting

Careful records of GMO experiments need to be kept. They provide documentation of the genetic modifications and verification data, observed phenotype, unexpected observations, and the like. This information is necessary for both preparing and evaluating an application for field-test release, as well as for documenting performance in the field. Records of all measures taken to comply with any conditions or risk-management measures imposed by the biosafety review committee may be useful for later reference. Regulators need accurate records to ensure compliance with risk-management conditions and redress in the case of accidental release. The biosafety review committee determines what information the applicant must record and the times at which the information must be submitted. These record-keeping parameters are then outlined in the approval document. Having collected efficacy data, applicants can easily neglect to forward risk-management records to regulators. Making the receipt of trial records a condition for review of subsequent applications is one way of ensuring that even the mundane risk-management records of uneventful trials are lodged as requested.

Risk-Management Realities

Some environmental risks can be reduced to an acceptable level by careful management. When biosafety reviewers determine that a proposed field test poses such a risk, they typically recommend that adjustments be made in the field-test release plan to address specific points of concern. For example, monitoring plans could be adjusted to be more comprehensive or provide different focus; contingency plans could be called for when early termination of the field-test release was seen as a distinct possibility; removal of an antibiotic-resistance marker gene before release could eliminate a concern that threatened to make approval unlikely; specific labeling could be created and attached to seed containers to reduce concerns about inadvertent mixing of GMO and non-GMO seed.

Such adjustments modify the risk potential of the proposed release and are a factor in the review committee's decision. Consequently, it is incumbent upon both risk assessors and applicants to be aware of management options that could be applied to a given field-test plan, taking into consideration not only science-based issues but also the policies of the regulatory authority and what measures are possible — scientifically and economically. Details of the risk-management requirements usually are appended to authorization documents issued for the field-test release.

In essentially every country, the costs of risk management are borne by the applicant. It is important, therefore, to ensure that risk-management requirements are in fact necessary and not just "nice to have." The cost of implementing risk management and the difficulty in meeting some specified conditions may lead applicants to postpone or cancel trials. This is especially true of publicly funded research in developing countries. Often biosafety frameworks are established in developing countries to prevent exploitation by outside interests and with the budgets of multinational companies in mind. This strategy can backfire when locally developed technology is ready for testing and public institutes are unable to afford the sometimes excessive requirements of over-cautious national frameworks.

An example is the indefinitely postponed marketing of fungal resistant strawberries developed in South Africa in the 1990s. Because the strawberries had performed extremely well in field trials, the national agricultural research institute planned to release them for commercial production. However, it has been unable to fund the food-safety tests required for commercial production. All three new genes in these transgenic plants are common in regular foods, and eight public juries believe the crop should be approved if labeled. However, the biosafety regulations require extensive toxicity, allergenicity, and nutrient testing before submission of a commercial application. As of late 2002, the status of the fungal resistant strawberries remains unchanged. The strawberries are maintained in tissue culture, but no additional work is being done with them. The public research institute can only wait until the genes have been approved in other crops and then request to use this safety data for their application. Interestingly, when presented with this case, most public juries are keen to eat the strawberries themselves to provide food-safety data.

5 Monitoring

Monitoring in biotechnology has different meanings and interpretations depending on individual perspectives or circumstances. In one sense, monitoring is the measuring and comparison of new plant varieties for relative performance and is a normal component of all stages of research and development. However, with the emergence of modern biotechnology, speculation about potential harm from GMOs introduced into the environment has shifted the focus of monitoring to following the fate of these organisms and the transgenes they carry and to be vigilant for unanticipated consequences.

Biosafety Monitoring . . .

- May contribute knowledge and experience in the use of organisms with novel traits
- Ranges from simple observation to extensive research studies
- Can be the responsibility of the "user" or an independent authority, organization, or body
- Can be used to verify assumptions made in a risk assessment
- Should be used to evaluate whether risk-management measures used are appropriate and effective.

—United Nations Environment Programme (UNEP), 1996

Background

Historically, monitoring programs in association with field-test releases of genetically modified organisms have been called for, explicitly or implicitly, as part of the regulatory agenda or as part of risk-management schemes. For example, in European Commission Directive 2001/18/EC[10] for releases of genetically modified organisms, Annex VII clearly describes the objective and general principles expected to be followed when developing a monitoring plan.

Voluntary compliance with monitoring programs (i.e., people did what they said they would do or what they were required to do) in the early days of field testing was encouraged by the notion that applications that incorporated monitoring into the experimental plan would be considered more favorably. Now, compliance with monitoring requirements is commonly ensured through reporting and follow-up field visits by regulatory authorities.

The Monitoring Paradox

"On one hand, new problems cannot be predicted and on the other hand if we can predict problems, they are not new. Wide-ranging, open-ended monitoring is probably the way to detect new or unique effects of genetic engineering. Yet such monitoring is expensive in time and money. It is also inefficient: surely most studies will find nothing at great expense even if a previously unknown problem eventually turns up. *It is helpful to decision makers and those who will be charged with the design and implementation of monitoring to know explicitly what should be monitored, the reason behind the concern(s), how monitoring should be carried out, and finally the purpose for data collected*" (emphasis added).

—K. Keeler, 1994

Monitoring Categories

EXPERIMENTATION

- Gather basic scientific information
- Test pre-release assumptions
- Improve experimental design

TRACKING

- Product development/marketing
- Regulatory compliance
- Incremental dissemination/dispersal

SURVEILLANCE

- Identified events
- Unanticipated impacts

When the first field tests of GMOs took place, it was not clear what should be monitored, why, or for how long. Monitoring objectives and methodologies were conceived and implemented with no precedent to follow and often resulted in unusable data or no data at all. Subsequently, methods and sampling designs have been refocused through experimentation to accommodate the large-scale releases of GM crops. For example, the issue of monitoring for the development of insect resistance to pesticides was raised as early as 1994 but did not become a major focus of risk-management programs until the commercialization of Bt crops. It is important to note, however, that the utility of monitoring programs is not restricted to answering biosafety concerns or indicating information gaps or the need for new assessments. Monitoring may also indicate a need for a different approach to regulatory or management decisions.

Biosafety Monitoring

Biosafety considerations are important in determining the need for monitoring, identifying appropriate target(s), and justifying the reasons for establishing specified levels of monitoring. Whether a GM crop or its DNA poses a safety concern if it should "move" into adjacent fields or to related plant species is an important environmental issue that raises the question of the extent to which transgene movement can or should be monitored. Furthermore, it necessitates the availability of efficient, accurate, and reliable methods of identifying transgenic material present in unintended locations.

Current methods include use of visual or selectable markers (e.g., β-glucuronidase, antibiotic resistance) or molecular analysis (e.g., PCR, Southern hybridization). Often the decision about what to monitor has depended as much on what is possible to monitor as on the identified concern. However, it is not possible to know what to monitor without knowing what potential problem might arise—the monitoring paradox.

Scales of Monitoring

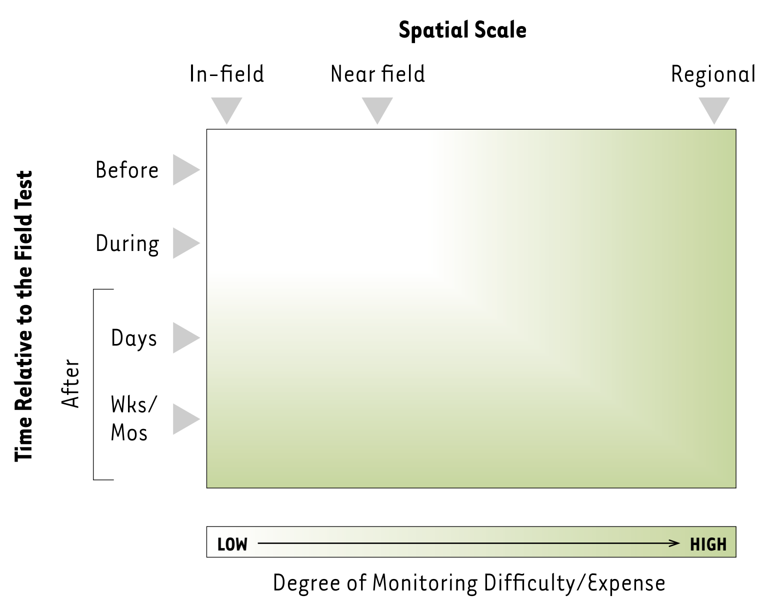
Monitoring programs fall into three categories—experimentation, tracking, and surveillance. The categories correspond, respectively, to the progressive scale-up in field-test, pre-, and post-marketing stages of product development.

Each successive stage brings different monitoring objectives and the need to consider larger geographic sampling areas and longer term observation regimes. Further, care must be taken in extrapolating experimental field-test monitoring results to commercial applications. For example, significant variations in gene flow measurements have been associated with increasing population size. The increasing temporal and spatial scales of monitoring programs is paralleled by an increasing difficulty to control and implement them (Figure 3). Similarly, the magnitude of potential adverse effect and the degree of uncertainty in the monitored parameter is mirrored by a need to increase the intensity of the monitoring program (Figure 4).

Experimentation

When field testing of genetically modified microorganisms first began in the United States, assumptions regarding monitoring needs led to ill-conceived and expensive protocols. Perhaps because little experience and no experimental evidence were available to draw upon, unproven methods were often chosen. During the course of field testing, it was discovered that these monitoring procedures were inadequate (i.e., inappropriately timed, provided poorly discriminated detection, or

Figure 3. Influences on the difficulty of monitoring. Spatial and temporal considerations influence the degree of monitoring difficulty and expense. Monitoring conducted early and near the test plot or large-scale field is relatively simple and cheap compared with later or longer term plans carried out over a larger area.



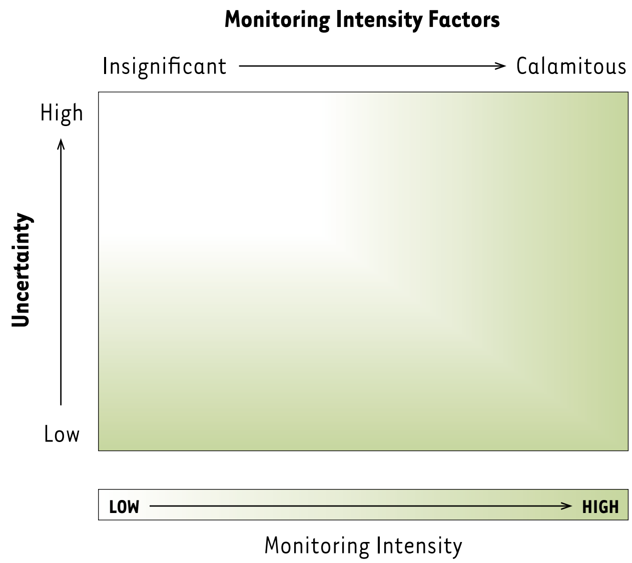


Figure 4. Factors contributing to the intensity of monitoring. The degree of uncertainty and magnitude of potential adverse effects determine the intensity of a monitoring plan.

naively conceived). The result was expensive monitoring schemes that produced little or no usable data. Research and field-testing experience led to the unfortunate conclusion that these early monitoring procedures would not answer the questions of concern. Experimenters and biosafety authorities must be aware that they will not always know the best monitoring approach at the outset. This argues for having a biosafety review process that balances concerns with the reality of scientific capability.

Tracking

Tracking refers to monitoring the movement and dispersal of organisms and their genes over time. If crop plants do not survive well beyond cultivated fields, tracking is not necessary. But if cultivated plots of crop plants have close relatives growing nearby, outcrossing of the engineered genes may be a concern. It is commonly recognized by breeders and agronomists that natural mechanisms for such outcrossing do exist. However, it is only in certain cases that a biosafety concern is raised (see "Scientific Issues for Environmental Risk Assessment," page 28).

Expanding the geographic range or duration of "sampling" beyond small-scale field tests poses significant difficulties for a comprehensive monitoring program. Assumptions about the best monitoring design and methodologies must be made on the basis of incomplete or insufficient information, despite what is often characterized as long-term experience with specific organisms and a full understanding of their growth characteristics. Episodic events at disparate intervals may produce very large differences in monitoring data. For example, the dispersal distance for oilseed rape pollen from commercial fields was measured at more than 150 meters as opposed to less than 10 meters from experimental plots. For events that have a very low probability of occurring, spatial and temporal expansion of monitoring protocols may be necessary to see gene flow when it happens.

Surveillance

Surveillance, the ongoing post-release observation of the organism to monitor its survival and dispersal or its environmental impact, is a form of monitoring appropriate when predetermined sampling regimes are impractical. However, devising a meaningful surveillance program presents difficulties when the environmental effects of a GMO release are only speculative. Furthermore, the large distances (e.g., kilometers) and long time intervals (e.g., years) associated with monitoring, for example, wind-driven pollen or seed dispersal may present technical difficulties in the design of sampling regimes. Large-scale surveillance may demand large numbers of people or large numbers of sampling sites and is likely to challenge even the most ample budget. Unfortunately, these factors may influence responsible investigators to suggest monitoring schemes based more on the availability of resources than on the collection of scientifically valid data that addresses a biosafety question.

When the United States Environmental Protection Agency granted a permit for the sale of insect-resistant Bt cotton, the agency required implementation of surveillance programs to monitor for the occurrence of increased insect pest resistance to the endotoxin of *Bacillus thuringiensis*. Upon evaluating the methods employed initially, the agency subsequently called for the use of more sensitive methods to increase the probability of early detection should resistance to Bt emerge in the pest population.[11]

Practical Planning

Monitoring procedures may vary from qualitative to quantitative, from simple to complex. We present a representative basic approach to designing a monitoring plan in Figure 5. The first step in

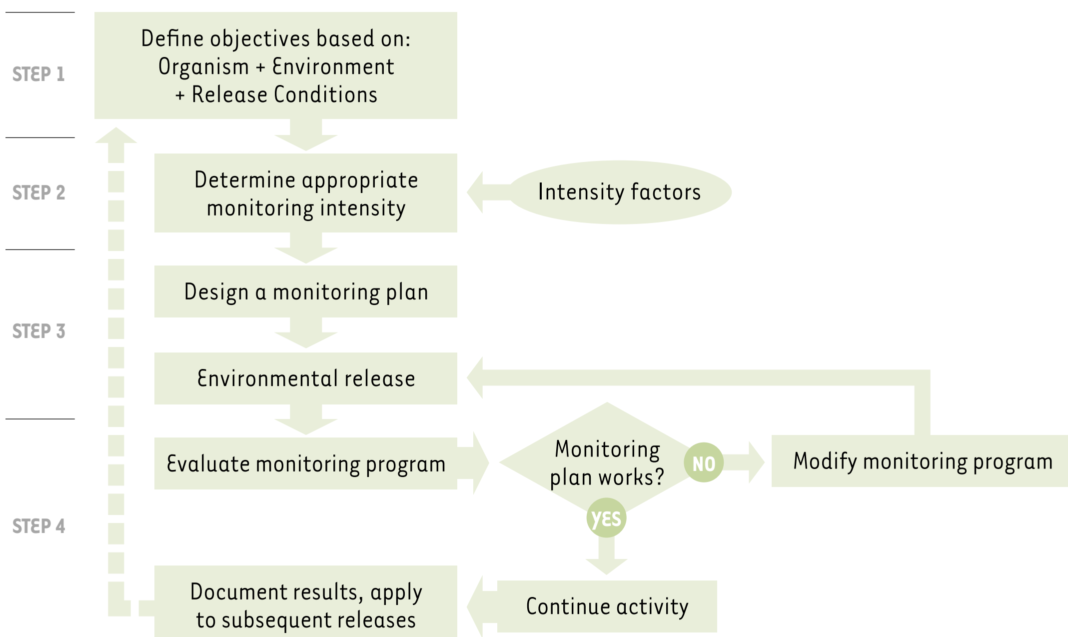


Figure 5. A basic approach to designing a monitoring program. The flow diagram depicts the process of designing and conducting a monitoring program.

Pitfalls of Monitoring

- Too much or too little effort given
- Unclear what to look for
- Doesn't go on "long enough"
- No appropriate mitigation available

—K. Keeler, 1994

planning a design is to define clearly the objectives of the monitoring plan, taking into consideration available knowledge of the organism to be released, the environment, conditions of the release (e.g., limited geographic area *vs.* open-market sales), potential risks as determined in a risk assessment, and regulatory requirements. The objectives of the monitoring plan determine the measurement endpoints. Integration of this information provides the basis for development of a specific monitoring plan.

The second step in a monitoring plan is to determine the appropriate level of intensity. Monitoring intensity is determined by the degree of uncertainty and the potential severity or probability of unwanted environmental impacts. The third step is to design the monitoring plan so that it includes specific sampling regimes and testing procedures. Step four is to evaluate the effectiveness of the plan after it is implemented. Thus it is important that monitoring plans be dynamic so that modifications can be made in response to changing conditions or unanticipated problems that might develop during the course of the program.

Biosafety assessors have an obligation to anticipate and avoid potential pitfalls in any monitoring design.

Ideally, a diverse collection of professionals will be involved in decisions about planning a monitoring program. These may include scientists conducting the research and development work, industry representatives concerned about financial soundness, legislators tracking constituency concerns, and regulators who claim jurisdiction. When working across professional boundaries, a risk assessor must learn to get results from diverse groups, which often requires finding a way to ask the question correctly and ensure that the right (trained) people are involved in the monitoring efforts. Cooperation (dialogue) among those involved is best begun even before applications are made and continued through data acquisition and analysis. The intent is not only to establish clear objectives, but also to ensure precise communication.

The risk assessor helps to ensure that adequate attention is paid to monitoring design and implementation. He or she needs to understand the monitoring objective and have some assurance that it is obtainable by implementing the monitoring design. If monitoring is intended as an environmental early-warning mechanism, there must be sufficient sensitivity to ensure the "alarm" is sounded in time to actually do something. A strategy must be in place for remediating an unwanted or unacceptable environmental impact, or, put more directly, there needs to be a plan describing what will be done should a crop be found going astray. It is equally important to distinguish between what is "nice to know" from what is "necessary to know." Monitoring programs not justified on the basis of risk simply waste resources, including the time of scientists and regulatory officials who will be obligated to review the irrelevant data collected.

6 Communicating about Risk and Biosafety

Introduction

As we stated at the beginning, biotechnology is a complex topic; it is a proposition with high stakes and has passionate proponents and opponents. Risk-assessment and risk-management procedures intended to identify and minimize potential negative effects on human health and the environment are key elements in making technical decisions to use, or not use, a product of biotechnology. However, just as a three-legged stool will not stand with only two legs, the public will not accept biotechnology as a tool for crop improvement until the third element — risk communication — becomes an integral part of biosafety procedures.

One of the most damaging lessons to emerge from the development of GM crops comes from early efforts to gain public acceptance of GMOs. When biotechnology products were first being field tested in the United States and Europe, public communications were seriously mishandled. Simplistic messages that oversold the technology (e.g., "biotechnology will put an end to world hunger"), dismissed people's concerns (e.g., "biotechnology is just an extension of what humans have been doing to improve crops for thousands of years"), or glossed over uncertainty (e.g., "I just don't think outcrossing will cause any problems") succeeded only in alienating an uneasy public. The private sector in particular transmitted an attitude of arrogance and deception that continues to undermine its credibility today, more than twenty years later.

Objectives of Risk Communication

Communication, not science, is the heart of risk communication. Regardless of subject matter and level of risk — whether reporting an outbreak of a devastating animal disease, announcing a GM crop field test, or talking to people living near a chemical spill — risk communication seeks to:

- Better educate the public about risks, risk assessment, and risk management
- Better inform the public about specific risks and about actions taken to alleviate them
- Improve communicators' understanding of public values and concerns
- Provide a mechanism for the public to voice concerns

"Danger is real, but risk is socially constructed."

—*P. Slovic, 1987*

- Increase mutual trust and credibility
- Reduce conflicts or controversies
- Promote transparency in the regulatory process

Part of the difficulty in communicating about biotechnology and biosafety is overcoming negative perceptions that already may be ingrained in public opinion. Common perceptions include:

- Companies put profit ahead of safety.
- Government regulators are either politically motivated, technically unqualified, or lack legitimate authority.
- Companies are untruthful in discussing risks and will lie if it serves their purposes.
- Scientists working in the private sector are unscrupulous or have been "bought."
- Developing countries are used as a dumping ground for products not approved elsewhere.
- The public is forced to assume the risk but gets none of the benefit.

It is important to note that some such perceptions do in fact arise from experience. Too often, however, public opinion about biotechnology is based on misperceptions of risk fueled by insufficient or inaccurate information. More fully informed opinions can arise only when people have a better and more realistic understanding of how biotechnology will affect their immediate lives and the environment in which they live. Risk communication is thus an important first step towards public dialogue concerning the development and use of GMOs. The following sections provide some of the basic rules for risk communication and offer practical guidance in communicating effectively.[12]

Principles of Risk Communication

Experience in communicating with the public about difficult topics such as toxic waste sites, immunization programs, and contaminated food incidents has provided some vitally important though sometimes painful lessons. These lessons can be distilled into basic principles of risk communication that have broad application to all areas of science and technology. Used wisely, they can help shape more meaningful and informative public communications.

Accept and involve the public as a legitimate partner

Contrary to proponents' initial expectations, the public has not enthusiastically embraced agricultural biotechnology. In retrospect, it is not hard to see how this came about. In the beginning, most scientists and, to a greater extent, company executives assumed that the wonders of biotechnology were self-evident and that the benefits were almost unlimited. They were slow to recognize that the public was becoming increasingly alienated by decision makers who ignored the need for public input into how the technology could or should be used, and they tended to underestimate or dismiss the public's concerns about safety.

More recently, policy makers, regulatory authorities, and GMO developers have started to change their way of thinking. They now see that providing a means for public involvement in decision making and paying attention to public concerns before they become adversarial issues are the first and perhaps most important steps in building public confidence in the safety of GMOs and acceptance of GM products.

How and to what extent this can be achieved will vary from one country to another. In the Philippines, representatives of nongovernmental organizations (NGOs) and public interest groups are members of the National Committee for Biosafety. By law, local communities where field tests are to be conducted must be notified in advance and given the opportunity to voice their position regarding the proposed tests. If public opposition is strong for whatever reason, the test may not be approved. At the other end of the spectrum, particularly in countries having nonparticipatory forms of government, there are no mechanisms for public input and it is not considered in official decision making.

Somewhere in the middle are countries, Argentina for example, where research scientists and national biosafety committee members engage in numerous formal and informal dialogues with environmental NGOs and consumer groups. In the United States, a public notice that an application for commercial production has been received by the Department of Agriculture's regulatory agency is published in the daily Federal Register. The announcement briefly describes the GMO, informs readers where to get full information about the proposal, and invites public comment within a specified timeframe (usually sixty or ninety days). During the subsequent biosafety review and in the ensuing decision document, all comments submitted by the interested parties are specifically addressed and responses given. In many countries, government regulators, biosafety officials, and scientists routinely appear in public discussion forums and, from time to time, organize informational meetings intended for general audiences.

Provide information through credible sources

People tend to pay attention to information coming from sources they trust. To a public hearing inconsistent and conflicting information about controversial issues, who the messenger is may be as important as the message. The "public" is not a homogeneous entity but rather a collection of numerous groups whose priorities and concerns are highly variable. To whom do different constituent groups turn for information? Who is viewed as a credible spokesperson? In some countries, government authorities may enjoy the public's full confidence. In others, authorities may not be well respected and may even be viewed with suspicion. Health care professionals and religious leaders often receive high marks for public trust. Industry representatives, particularly those from large multinational companies, are very often seen as being among the least trustworthy sources. Among differing cultures, farmers, scientists, extension officers, teachers, and community leaders may have greater or lesser credibility with the public at large. Information campaigns are likely to have greater impact when trusted sources are identified at the start and enlisted to deliver information to the target audiences.

Be honest, frank, and open

No single person has all the answers. Communicators build trust and credibility with their audience by acknowledging when questions go beyond their knowledge and offering to find the information and provide it later. Perceptions are extremely important; if the communicator appears honest and sincere, what he or she says is perceived as honest and sincere.

Because culture and personal values are ingrained within us, it is very difficult for any one

individual to be totally without bias. Having more than one communicator on hand, preparing remarks in advance, and having speakers and listeners cross-check to make sure what is being said and what is being heard are the same can lessen the impact of personal bias.

Be proactive

Uninformed consumers are more receptive to inaccurate, biased, or inflammatory messages than those who have some knowledge about GMOs. A balanced and realistic information strategy needs to be implemented *before* misinformation from other sources takes root in public opinion. Having to react hastily to antibiotechnology actions and rush to repair the damage is often too little, too late.

Risk Communication in Practice

Provide clear and accurate information. In communicating about biotechnology to a nontechnical audience, information needs to be translated into everyday language. Explanations using ordinary words can help the public gain more realistic ideas about the technology — what it is, what benefits it offers, what concerns it raises — and how it is being used. For instance, the subject of DNA can be introduced with an analogy to videotape: both are linear and carry information that must be decoded. Genetic engineering can be viewed as similar to editing videotape. Like videotape, DNA can be cut and spliced back together; it can be copied; segments can be removed, duplicated, or moved to another position; segments from different sources can be combined into one; pieces can be put in reverse orientation, and so on.

Through experience, a number of useful observations have emerged. Among these are:

- There is no one-size-fits-all talk suitable for all audiences. Knowing who the audience is and what their concerns are allows speakers to deliver information focused on subjects most important to them.
- In talking about benefits and risks, good communicators strive to present balanced, credible information that seeks to inform, not convince, the audience.
- Legitimate concerns posed by certain combinations of crop-trait-location deserve to be acknowledged and, where possible, applicable risk-management strategies can be described.
- A balanced discussion of potential risks includes consideration of the risks of not using the technology, choosing instead to continue current practices.
- Statements presented as fact will have more credibility when supported by documentation that can be verified.
- Good communicators are wary of the tendency to speak authoritatively about a subject on which actual knowledge lies somewhere between experimentally proven fact and personal belief. (Presenting speculation as fact and drawing major conclusions from irrelevant, out-of-context, or untrue "facts" are transgressions commonly committed by groups opposed to the use of biotechnology.)
- No one knows everything. It is only sensible to acknowledge that for some questions, the answers are not known.

Listen to your audience

People attending any kind of discussion forum generally want to either learn more about the subject, express their opinion, or both. Effective communicators make it a point to find out what their audience wants to know and are prepared to provide that information. They give people an opportunity to speak without being judged and pay attention to what is said. Experts in conflict management stress that making the effort to hear someone's concerns and showing that they have been heard and understood are critical to ensuring that an issue is resolved.

Biotechnology can stir up strong feelings in many people, even though they themselves may not be able to pinpoint the root cause. When commenting on a given subject, they may start out calmly but become increasingly angry or accusatory as they address more and more issues. In these difficult situations, it is worth remembering that the speaker is not really looking for immediate solutions, but needs to feel that his/her concerns are being heard.

Understand our human nature

Many of the public's concerns about using GMOs seem to derive from a lack of data that would "prove" safety or at least absence of risk. The implication is that if sufficient scientific information became available, public concerns would likely subside. Although there may be some truth to this simple explanation, attitudes about biotechnology are significantly complicated by ordinary human attitudes and perceptions including the following.

Fear of the unknown

No one can predict what long-term effects might arise from growing GMOs and eating GM foods. Past cases of unanticipated or delayed harmful consequences arising from new technologies and products touted as safe (e.g., use of broad-spectrum synthetic pesticides, introduction of exotic species, or ground-water contamination by agrochemicals) have made consumers much more cautious.

Resistance to change

Change takes energy and causes discomfort until people become familiar with the new situation. Traditional farming methods are seen as an icon for a simpler, purer kind of existence.

Inaccurate perceptions of risk

Studies measuring human perceptions of the relative riskiness of certain activities or behaviors (medical x-rays, cigarette smoking, riding in a car, use of pesticides, and the like) reveal wide discrepancies between those perceptions and statistical data.

Unrealistic expectations

Where uncertainty exists, many people want, and some demand, a guarantee of zero risk or absolute "proof" of safety. Both are impossible.

Recognize that the debate is not about science alone

Biotechnology has several unique features that raise powerful concerns not associated with conventional agriculture: its capacity to manipulate the very nature of living things in unprecedented ways; its use of patents and other means of intellectual property protection that severely limit access to its products; its identification with large multinational companies that are seen as the nemesis of small farmers, particularly in developing countries; and its added costs for regulatory compliance and patent protection that make it unaffordable to poor farmers. Addressing only the scientific issues will have limited impact on public acceptance because, unlike conventional research methods, biotechnology triggers deep-rooted social, economic, and ethical concerns.

Trust

Government agencies lose credibility when the public learns, belatedly, they were misled about the seriousness of a hazard or not fully informed about a hazardous incident. A prime example is the mishandling by government officials in the United Kingdom of the outbreak of "mad cow" disease, first by denying the disease was present and then by grossly underplaying the extent of its spread and the number of people affected. The public, having found government authorities to be untrustworthy in the past, now is disinclined to believe their assurances of safety with respect to biotechnology. Within the private sector, many of the leading biotechnology companies are considered highly untrustworthy because of their record of mishandled public relations that oversold the benefits, denied any sort of risk, and dismissed consumer concerns as irrelevant.

Control

The ongoing consolidation of the agribusiness sector, marked by a trail of industry mergers and acquisitions that have created megamultinational corporations and caused the disappearance of many smaller seed companies, leads many people to feel that important decisions and choices are being taken away from them. Consumers feel they are losing control over what they eat. In major GMO-producing countries such as the United States and Argentina, standard commodity-handling procedures result in a mixing of GMO and non-GMO varieties of corn and soybeans. As a result, a high percentage of processed foods made with corn or soy ingredients have some GMO content. Consumers insisting that GMO-containing foods be labeled are reacting to their loss of control over the choice to buy or not buy foods derived through biotechnology.

From farmers' point of view, companies are exercising increasing control over their choice of what to plant and how to manage their farms. Unlike commercially sold or publicly held conventional varieties, GM varieties carry patents that restrict farmers' ability to save seed for replanting or to sell or trade it with other farmers. Some transgenic crops engineered with a Bt gene for insect protection are subject to planting restrictions that require the farmer to grow a specified percentage of non-Bt seed at the same time. These developments reduce farmers' options and tend to make them increasingly dependent on the seed companies.

Equity

Biotechnology raises fundamental questions about the equitable distribution of its benefits. Private-sector companies seeking profits are propelling advances in crop quality and productivity, whereas public sector research to improve the status of resource-poor farmers lags far behind. Almost all commercialized GMOs to date are crops and varieties that are economically important in developed countries but poorly adapted or unsuitable for use by farmers in developing countries. Access to improved seed is not uniform; small-scale and subsistence-level farmers in developing countries cannot afford the associated costs.

Simple fairness holds that in any undertaking having an element of uncertainty, those who accrue the benefits should bear the risks. This has not been the case for biotechnology and GM products. Many people feel that they, not the companies, are being

asked to assume the potential risks of negative environmental and health impacts from products that have no direct benefit for them. Although the situation is likely to change as more consumer-oriented products reach the market, the perception of inequity has impeded public acceptance.

Morality and Ethics

The power of biotechnology to manipulate the genetic makeup of a plant or animal in ways that do not appear to occur "naturally" may conflict with some people's religious beliefs and innate sense of right and wrong. Some see the ability to cross species barriers as tampering with things with which humans ought not to interfere, a form of playing God. Further, the public's low level of scientific understanding to some extent leads to a perception of biotechnology in which genetically engineered crops lie within a continuum of research that leads inevitably to the cloning of human beings.

Identify and train communicators

Good communications skills are the hallmark of effective spokespersons. They are comfortable meeting and talking with the public and the press. They are able to convey complex ideas in simple yet accurate words. They have good listening skills and pay attention to what others are saying. Good communicators distinguish between what is known as fact and what is believed but speculative. They are able to respond point by point to a wide range of questions, criticisms, inaccuracies, and accusations without resorting to heated or antagonistic words. They are able to calmly point out false, misleading, or unsupported statements and correct them with an even-handed response that can be substantiated. They avoid being distracted by comments or questions not relevant to the topic at hand. They show a sense of humor, admit fallibility, and claim their own role as consumer, concerned citizen, and part of the public.

These skills can be learned. The field of risk communication has produced a substantial literature on the principles and methods of responding to public concerns that is adaptable to many subject areas. Institutions including regulatory agencies can seek to identify those who would make effective spokespersons and support their skills development through risk-communication training.

Meet the needs of the media

Media's main purpose is to sell newspapers and attract viewers and listeners. Media act as filters of information by being selective about what is published or broadcast. To help keep a story alive, media present different views on controversial issues as being equally valid or as having equivalent support in the larger community. When the subject is biotechnology, too often articles with sensationalized headlines, frightening misstatements of fact, wild extrapolations, and baseless pronouncements win out over sober reporting that distinguishes clearly between what is known by science, what is reasonable speculation, and what cannot be supported by any evidence.

Regardless of whether the reporting is accurate, biased or erroneous, the media are the public's primary source of information about biotechnology. Reporters are unlikely to be knowledgeable about GMOs and may know little about science. Accordingly, media education is important in promoting informed discussions on the merits and concerns associated with biotechnology.

Communicators, especially official spokespersons who regularly speak to the media, are well advised to keep messages brief, clear, and to-the-point. Repeating the most important statements in exactly the same words helps reporters remember them correctly and may provide a useful quote.

Experts in risk communication advise spokespersons never to assume that reporters or media representatives are neutral, independent, sympathetic to you, objective, or altruistic. Nor should spokespersons assume that reporters are devious or dishonest. All parties benefit when members of the biotechnology community cultivate cooperative relationships with reporters and editors. They can do this by making themselves readily available for interviews, accommodating media deadlines, and being prepared to provide names of other resource people knowledgeable about biotechnology, GMOs, environmental issues, food safety, regulations, and related areas.

Notes

1. "Cartagena Protocol on Biosafety to the Convention on Biological Diversity." 2000. Adopted at the Convention on Biological Diversity, January 29, 2000, Montreal, Canada. *http://www.biodiv.org/biosafety*
2. *http://www.biodiv.org/biosafety*
3. United Nations Environment Programme (UNEP). 1996. *UNEP International Technical Guidelines for Safety in Biotechnology*. Nairobi, Kenya: UNEP.
4. "Cartagena Protocol on Biosafety to the Convention on Biological Diversity."
5. "Directive 2001/18/EC of the European Parliament and of the Council (on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/20/EEC." *http://biosafety.ihe.be/GB/Dir.Eur.GB/Del.Rel./2001_18/2001_18_TC.html*
6. Mocrobes are exposed to root exudates and plant debris remaining in the field after the end of the growing season.
7. Australia New Zealand Food Authority (ANZFA). 2000. "GM Foods and the Consumer." ANZFA Occasional Paper Series No. 1. *http://www.anzfa.gov.au*
8. Traynor, P., Adair, D., and Irwin, R. 2001. *A Practical Guide to Containment: Greenhouse Research with Transgenic Plants and Microbes*. Blacksburg, Virginia: Information Systems for Biotechnology.
9. *http://www.aosca.org*
10. "Directive 2001/18/EC of the European Parliament and of the Council."
11. U.S. Environmental Protection Agency, Office of Pesticide Programs, Biopesticides and Pollution Prevention Division. 2001. "*Bacillus thuringiensis* (*Bt*) Plant-Incorporated Protectants." Biopesticides Registration Action Document, October 15, 2001. *http://www.epa.gov/oppbppd1/biopesticides/otherdocs/bt_brad2/4 irm.pdf*
12. Some of the material is based on the work of Peter Sandman, a leading consultant in risk communication, and Vince Covello, Center for Risk Communication, New York.

PART TWO

Case Study Exercises

Introduction

Hands-on practice is an effective way to build the competence and confidence of biosafety reviewers. In these case study exercises, participants assume the role of a national biosafety committee member and critically evaluate proposed releases of genetically modified organisms (GMOs). The exercises will:

- Familiarize participants with representative application documents
- Illustrate a deliberate step-by-step process for conducting risk analyses
- Demonstrate the linkage between risk assessment and risk management
- Recognize important distinctions between safety and nonsafety issues
- Challenge participants to think critically

Each case consists of:

- A detailed "application" document that describes the biology and ecology of the recipient crop species, the introduced trait or phenotype, inserted genes and genetic elements and their sources, the field-test site, relevant information pertaining to potential risks, procedures and management practices that differ from the standard, and other information that may (or may not) be relevant.
- A worksheet to assist in analyzing the application. Participants will record:
  - Safety concerns associated with the inserted genes, methodology, resultant phenotype, local environment, experimental design, and procedures *with regard to safety,* and other safety issues raised by the proposed release
  - A summary of the group's findings on identified risks and risk-management strategies
  - Nonsafety issues raised by the proposed release
  - Technical, financial, and human resources needed to conduct the review and ensure compliance

At the instructors' discretion, some cases will be analyzed in the classroom with open discussions and guidance from the instructors; some may be completed outside the classroom.

For some exercises, participants will work in country groups so they can consider their own national context for biosafety and biotechnology in agriculture.

Some exercises will include preparation of a decision document to record and justify the decision taken (approved, deferred, or denied) and the conditions or requirements imposed upon the applicant.

In cases that are recommended for approval, participants will prepare a public notice in ordinary language explaining what the GMO is and why it has been found not to pose an unacceptable risk. In cases that result in a recommendation to deny the request, participants will prepare a brief explanation in ordinary language of why it was not approved.

Instructions

NOTE: Each group first should establish terms of reference with regard to the *purpose* and *scope* of its work as a biosafety review committee (15 minutes). See pages 11–15 of Part One of this workbook for further details on terms of reference.

A. Read the case-study application proposing release of a GMO to the environment. For the purpose of these exercises, *assume* that data referred to in the text, but not found in the case document, were submitted with the application.

B. Evaluate the proposal in the step-by-step procedure outlined below. Use the worksheets provided to record the group's findings.

1. Identify genes and other DNA sequences inserted in the recipient organism, their source of origin, and the resultant phenotype(s).
2. List key details of the proposed release pertaining to the nature of the crop species, introduced trait(s), and local environment.
3. Identify potential risks arising from crop-trait-environment interactions.
4. List questions to be asked of the applicant for clarification.
5. Determine if the information provided is sufficient; describe what is missing.
6. Assess the probability and potential consequences of any identified risk.
7. Identify proposed risk-management procedures and evaluate their adequacy.
8. Determine what conditions or restrictions should be imposed and why.
9. Specify monitoring and follow-up procedures, if indicated.
10. Recommend a response to the application and justify it.

C. Using the worksheets provided, answer the following questions:

1. What nonsafety issues are raised by the proposed release?
2. What scientific expertise is needed to review the application?
3. What resources are needed to meet the conditions and requirements for approval?

CASE STUDY 1: Application for Greenhouse Trials with *Ralstonia* Genetically Modified for Biocontrol of Bacterial Wilt in Potatoes

1. Brief Description of Proposed Trial Release

Ralstonia (syn. *Pseudomonas) solanacearum* causes bacterial wilt in potatoes in Sub-Saharan Africa. This disease is growing into a serious limiting factor in the production of potatoes in the area. The loss of this industry will have serious economic impact for the region. The disease affects both commercial and small farmers. Laboratory experiments with insertion mutants of biovar2 strains of the pathogen have shown considerable biocontrol activity against wild type strains of the pathogen. It is now necessary to test the genetically modified biocontrol strains in more representative soil conditions, but this is not currently possible in Africa because these countries do not yet have biosafety structures to assess the risk parameters for greenhouse trials. For this reason, the applicant seeks to conduct greenhouse trials in South Africa because its climate more closely reflects African environmental conditions than the applicant's research facilities in Europe.

2. Objective

2.1 What is the aim of the proposed trial release of the genetically modified organism (GMO)? What are the benefits of this approach compared with other possible methods, especially those not involving planned release?

The modified bacterial strain will be tested for its effectiveness in controlling pathogenic wild type strains. Current control measures require that affected fields be left fallow for two to three years, but this causes significant economic loss and hardship to African farming communities.

2.2 If the trial release is successful, do you intend to propose a general release of the GMO?

Yes.

If so:

2.2.1 When do you propose that the general release would take place?

Only once regulatory frameworks are working in African countries.

2.2.2 Where do you propose that the general release would take place?

Sub-Saharan Africa. However, if effective against local bacterial strains, a general release may of interest to local agriculture agencies.

2.2.3 By whom do you propose that the GMO would be released?

Local agricultural agencies.

2.3 Do you intend to market the GMO as a product in this country?

Possibly, depending on how effective it is for local disease management.

3. Nature of Organism and Novel Genetic Material

3.1 What is the species of the GMO to be released?

A nonpathogenic mutant of the bacterium *Ralstonia solanacearum.*

3.2 Do the unmodified form(s) have any adverse effect on:

3.2.1 Humans, animals, or plants?

No.

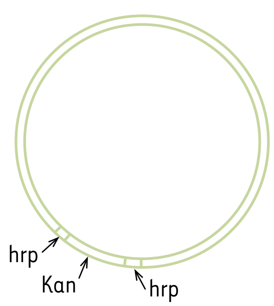
3.3.2 Agricultural production?

No.

3.2.3 Any other aspect of the environment?

No.

3.3 Furnish a description of the genetic, and resultant phenotypic, modifications of the GMO. This should include the origin of the inserted DNA, the procedure used to induce the genetic modification, and the extent to which it has been characterized.



Map of the omega cassette that was used to disable virulence in *Ralstonia*

KEY

hrp = target sequence for crossover insertion into the *Ralstonia* virulence region

Kan = kanamycin resistance gene

Gene insertion was used to knock out the virulence gene in the wild type strain. The inserted DNA, the omega cassette on plasmid pKhrp42a, consisted of a kanamycin resistance gene (*npt II*) flanked by short segments of the *hrp* gene which targeted the insertion to the virulence region. Wild type bacteria were transformed using standard procedures and transformants were selected on kanamycin-containing medium. The stability of the inserted DNA was tested over many generations on selection and nonselection medium.

3.4 What is the frequency of reversion, i.e., loss of genetic modification?

None.

3.5 How do you verify that you have the desired GMO?

Km resistance.

3.6 What methods will you use to test for batch-to-batch consistency?

Molecular fingerprinting.

3.7 On the basis of contained experiments, describe:

3.7.1 The survival rates of the GMO in the spectrum of conditions that are likely to be found in the proposed release area(s) and surrounding environment(s)

The mutants survive for long periods in laboratory conditions. Experiments monitoring GMO survival in soil indicated that they decreased rapidly in the numbers of GMOs in the first week, but then a stabilizing of the population at very low counts (approximately 10^{-17}) for the duration of the monitoring, which was six months. However, current control mechanisms indicate that wild type numbers decrease in fields not planted with potatoes. After two to three years, the numbers are low enough to enable farmers to plant potatoes without fear of infection. This will need to be tested to the GM strains in future field trials.

3.7.2 The capability of the GMO to disperse from the release area and the dispersal mechanisms

Containment conditions will be imposed to prevent dispersal of the GMO from the greenhouse.

3.7.3 Any other relevant information. (If reports or publications are available for any of the above information, please furnish copies or references.)

N/A.

3.8 If, at any stage in the future, biosafety regulators need to ascertain whether the GMO is the same as the GMO specified here, what means are available?

Km resistance; hybridization; molecular fingerprinting.

3.9 Provide a protocol and materials to enable detection of foreign gene(s) in surrounding microbial, plant, or animal life.

This protocol is a trade secret, but we will carry out identification tests on samples provided by the regulators and enable the regulators to police the detection results by providing blind positive samples.

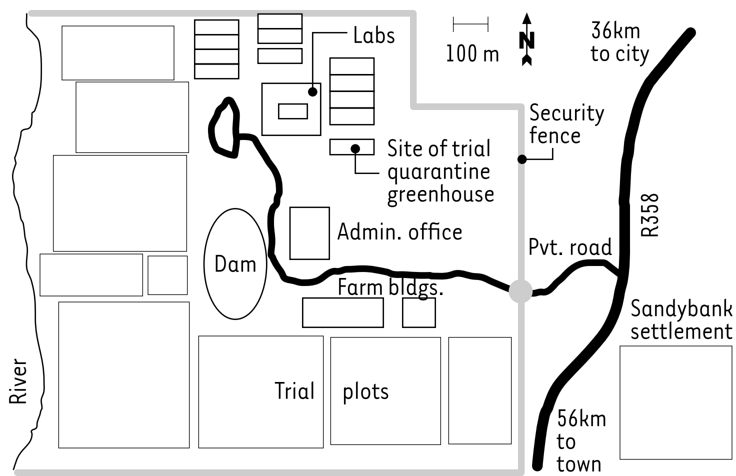
4. Trial Release: General

4.1 Full details are required about the manner in which the trial release of the GMO is to be undertaken. The following aspects, at least, should be addressed:

4.1.1 The location of the site for the proposed released (e.g., ordnance survey map of appropriate scale with site marked)

A quarantine greenhouse at the National Agricultural Research Institute, address given and map attached.

Map of the trial site at the National Agriculture Research Institute



4.1.2 A description of the test site in terms of:

Size	30 sq. m
Soil	Lawn and trees surround the greenhouse. Soil is loamy.
Groundwater level	Water table 13 m below ground.
Topography	Undulating hills.
Flora and fauna	Situated in an agricultural area with interspersed natural bush vegetation.
Climate, especially prevailing winds	Temperate, highlands. Moderate spring and summer winds predominantly from the southwest.
Former use	The greenhouse is routinely used to quarantine imported or experimental plants.
Distance from nearest human settlements	1.3 km from an informal housing settlement.
Distance from surface waters	500 m from irrigation dam, not in catchment area. One km from river. Rainwater runs past greenhouse complex towards river. Very gradual slope of about 10 m in 1 km.
Distance from environmentally and otherwise protected areas	50 km to nearest recreational and natural site.

4.1.3 A description of the environment immediately surrounding the release site

Lawn and trees.

4.1.4 The barriers planned to segregate the experiments constituting the trial release from the surrounding environment

Glass, netted air vents, treated water catchment.

4.1.5 The supervision and monitoring of the trial release

Daily supervision and monitoring; kept locked.

4.1.6 The contingency plans to deal with extreme conditions such as storms, floods, and bushfires during the course of the trial release

Shadow netting protects against hail. The research facility has standard emergency facilities for fire and floods.

4.1.7 The provisions to remove or eliminate the GMO from the test site or any other place where it may be found upon completing the trial release and to restore the test site and any such other place to its status quo.

The soil, pots, and plants from the trial will be autoclaved and the room will be sterilized with a fog of hypochlorite.

4.1.8 The arrangements for producing the GMO in quantity

In liquid broth and on agar plates.

4.1.9 The arrangements for transporting the GMO to the release site

Will be carried from the nearby laboratory.

4.1.10 The quantity of the GMO to be released

Approximately 10 ml per plant; total 400 ml.

4.2 What potential hazardous or deleterious effects resulting from the trial release of the GMO can be postulated?

Transfer of the omega cassette to other living organisms.

4.2.1 Which of these effects are to be monitored and evaluated during the trial?

Transfer of the omega cassette to other living organisms will be monitored during the greenhouse trial.

4.2.2 How are these effects to be monitored and evaluated during the trial?

Km resistance in other bacteria seeded into the sterile soil.

4.2.3 If some effects are not going to be monitored, why not?

4.3 Have similar releases of similar GMOs been made previously, either within or outside this country?

Yes, a similar greenhouse trial was carried out in France.

If so:

4.3.1 What were the beneficial consequences?

Statistically significant pathogen control.

4.3.2 What were the adverse consequences?

None. No transfer of the omega cassette to seeded bacteria in the soil was detected.

4.3.3 What factors might suggest a greater, or a lesser, risk for adverse consequences for the now-proposed trial release? (Provide references or reports to support your statements.)

Nothing. The trials will have similar risks. Greenhouse trial report supplied in appendix.

4.4. Have similar requests or applications for the release of this particular GMO been made before?

No.

4.4.1 Where was the application made?

N/A

4.4.2 What was the result?

N/A

4.5 Is there any evidence that the inserted genetic trait is transferable to other organisms in the release site and surrounding environment?

Although transfer may be remotely possible, it has not yet been observed in similar trials.

4.6 What data are available to suggest that the introduced genetic trait has no deleterious effect in the long term upon the species into which it has been introduced or allied species or any other organisms or the environment in general?

No data available.

4.7 Is the GMO intended to modify the characteristics or abundance of other species?

No.

4.8 What experimental results or information exist to show the probable consequences (positive and negative) of the release of such a modified organism, including impacts on:

4.8.1 Human, animal, or plant health?

None, except the decrease in bacterial wilt disease in potatoes.

4.8.2 Agricultural production?

Control of bacterial wilt in potatoes. Long-term increase in potato production. Decrease in bacterial wilt pathogen population.

4.8.3 Target and nontarget organisms in the area?

No potatoes are planted near the greenhouse site, but related bacteria may exist in the soils around the site.

4.8.4 The general ecology, environmental quality, and pollution in the area?

None.

4.8.5 The genetic resources (e.g., susceptibility of economically important species to herbicides, pesticides, etc.)?

No additional impact is expected.

What is your assessment of the possible effects?

Km resistance genes and many transposable mutant elements are naturally present in soils. The addition of a small amount of additional genes that quickly decrease to natural soil levels is not likely to have any greater effect on genetic resources than naturally occurring gene transfers in soil already have.

4.9 Will the trial release have any unlikely but possible impacts?

No.

4.10 What will be the consequences if the organism remains in the environment beyond the planned period?

None. The greenhouse and equipment will be disinfected with the standard protocols used to eliminate potentially pathogenic microorganisms.

4.11 Has a trial release been carried out in the country of origin of the GMO?

No. The bacterium is a Central African isolate.

4.11.1 If not, provide reasons why the trial release was not carried out.

No biosafety review process is available in these countries.

4.12 Provide a draft copy of a press release informing the public of the trial or general release of the GMO.

Attached.

5. Trial Release: Microorganisms Associated with Plants

5.1 What is the target species of plant?

Solanum tuberosum (potatoes).

5.2 Is the organism able to establish itself on/in nontarget species in the surrounding environment?

Not known, but possibly.

5.3 To what extent does the organism survive and reproduce on/in:

5.3.1 The target plant?

The GMO is a common pathogen of potatoes and survives effectively in potato fields. However, it decreases to nonpathogenic levels if the fields are not planted with potatoes for two to three years.

5.3.2 The rhizosphere of the target plant species?

See 5.3.1.

5.3.3 Other plant species in the test site?

There will be no other plants in the release area.

5.3.4 And surrounding environment?

Not known.

5.4 What characteristics do you intend to impart to the target plant species?

None.

5.5 Can these characteristics be imparted to nontarget plant species, especially those in the surrounding environment?

No.

5.6 In the case of soil organisms, what are the likely effects on organisms in the test area that are known to be beneficial to plants (e.g., *Rhizobium, Frankia,* and mycorrhizal fungi)?

Ralstonia is not a dominant species unless potatoes are growing in the soil. While DNA can transfer between soil organisms, the genes are already endemic to most soils.

5.7 In the case of soil organisms, what are the effects expected on soil chemistry (e.g., pH, mineral leaching, chelation, nutrient levels)?

None.

6. Trial Release: Microorganisms to Be Used for Modifying the Environment (e.g., biological control, pollution control)

6.1 In the case of biological control organisms, what is the biological control target species?

Ralstonia solanacearum, biovar 2.

6.2 What direct effects do the unmodified and modified organisms have on:

6.2.1 The target species?

The modified organism prevents or reduces colonization of plant by nonmodified organisms.

6.2.2 Nontarget species (including humans)?

The GMO is nonpathogenic, but the wild type causes bacterial wilt on potatoes.

6.2.3 Any plant or animal species being protected from the target species?

None.

6.3 What is known about the organism's ability to survive and reproduce in association with the target species or substance?

Survival is not enhanced. The wild type pathogen is less effective at colonizing potatoes when the GMO is present.

6.4 Can the organism establish itself in association with nontarget species or substances?

No known occurrence has been reported.

6.5 Does the organism produce metabolites that may have deleterious effects directly on other organisms or indirectly through concentration in the food chain?

No.

6.6 Can the modified genetic traits be transmitted to other microorganisms that are likely to be in the environment?

Although this is remotely possible, no evidence of such transfer has been found in numerous laboratory studies designed to optimize such transfer.

6.7 What genetic response might be invoked in populations of the target organism as a result of the use of the modified organism (e.g., increased resistance to the modified organism)?

None.

CASE STUDY 2: Application for Greenhouse Trials with Sunflower Genetically Modified for Fungal Tolerance

1. Brief Description of Proposed Trial Release

Modifications to sunflower (*Helianthus annuus*) have increased tolerance to fungal infections. Fungi such as *Sclerotinia* and *Fusarium* cause approximately US $150 million loss per year to the sunflower industry. Growth in greenhouse facilities is required to determine whether pollen from *H. annuus* can pollinate local *Helianthus* relatives. Sunflowers are pollinated by bees and thrips. These insects will be located in the greenhouse and the conditions will be optimized for pollination to occur. In addition, some plants will be hand pollinated. The seed will be collected and transferred back to the laboratory for routine analysis. The data from this experiment will be used to determine safety conditions for future field trials with GM sunflower and to identify areas where additional biosafety research will be needed to assess adequately the GM sunflower's potential impact on wild relatives.

2. Objective

2.1 What is the aim of the proposed trial release of the genetically modified organism (GMO)? What are the benefits of this approach compared with other possible methods, especially those not involving planned release?

Greenhouse pollination studies are needed to assess whether pollen from commercial sunflowers is sexually compatible with local relatives of the crop. These data are essential to determine the risk of gene flow from GM sunflowers into natural flora.

2.2 If the trial release is successful, do you intend to propose a general release of the GMO?

The greenhouse data will help establish confinement conditions for field trials with the GM sunflower. The efficacy of the fungal tolerance modification will need to be determined in field trials before decisions will be made about whether or not to commercialize the GM crop. Certainly, the greenhouse trial is one step towards the development of a commercial crop.

3. Nature of Organism and Novel Genetic Material

3.1 What is the species of the GMO to be released?

Helianthus annuus — sunflower.

3.2 Do the unmodified form(s) have any adverse effect on:

3.2.1 Humans, animals, or plants?

No.

3.2.2 Agricultural production?

No.

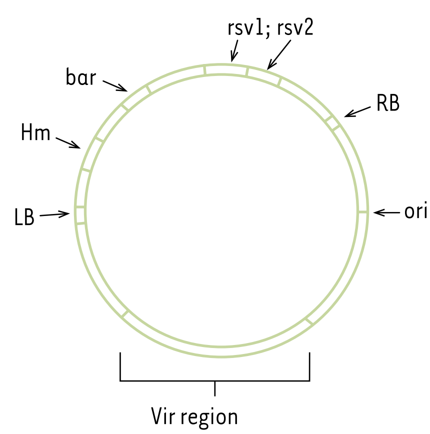
3.2.3 Any other aspect of the environment?

No.

3.3 Furnish a description of the genetic, and resultant phenotypic, modifications of the GMO. This should include the origin of the inserted DNA, the procedure used to induce the genetic modification, and the extent to which it has been characterized.

The sunflower was transformed by agro-infection using a construct that contains an antibiotic marker (resistance to hygromycin), an herbicide tolerance gene (the bar gene giving tolerance to Basta), and two resveritol genes from grapevines, giving tolerance to fungal infection. The antibiotic marker gene and the herbicide tolerance gene both come from soil organisms. A single, stable insertion has occurred in one of the plant chromosomes.

Map of the disarmed *Agrobacterium* Ti-plasmid used to transform sunflower



KEY

LB-RB = T-DNA transferred to sunflower

Hm = hygromycin resistance gene with nos promoter and terminator

bar = phoshinothricin tolerence gene with 35S promoter and nos terminator

3.4. What is the frequency of reversion, i.e., loss of genetic modification?

None detected in stable transformants.

3.5 How do you verify that you have the desired GMO?

PCR analysis for the three inserted genes.

3.6 What methods are to be used to test for batch-to-batch consistency?

PCR analysis.

4. Trial Release: General

4.1 Full details are required about the manner in which the trial release of the GMO is to be undertaken.

The plants will be grown in a contained greenhouse on the roof of the university's Life Science Building. Provision will be made for insect and manual pollination to occur. Manual pollination is usually required where ploidy differences occur between related species. Locking the facility will control access, and all waste will be autoclaved after the experiment. The facility will be disinfected after the conclusion of the trial. Seed will be collected and transferred to the laboratory for further analysis.

The following aspects, at least, should be addressed:

4.1.1 The location of the site for the proposed released (e.g., ordnance survey map of appropriate scale with site marked)

The greenhouse is designed for entomological work and is situated above the entomology department on the roof of the six-floor Life Sciences building. Access is via a restricted elevator. Only senior staff hold elevator keys to the roof floor.

4.1.2 A description of the test site in terms of:

Size	12 sq. m greenhouse.
Soil	None in the immediate area. Ground around the building is mostly paved with a few small plant boxes for gardens.
Groundwater level	Water table is 33 m below ground.
Topography	The university is situated on the top of a hill in a high-rise city environment.
Flora and fauna	The flora and fauna are typical of an urban environment: little biodiversity and mostly exotic species.
Climate, especially prevailing winds	Temperate. High (3,000 m above sea level). Moderate winds. Some summer storms with hail.
Former use	The greenhouse is routinely used to quarantine imported biocontrol insects for assessment on local pests.
Distance from nearest human settlements	300 m from the university boundary, which borders a dense residential area of mostly high-rise apartments.
Distance from surface waters	The nearest surface water is a stream at the bottom of the campus about 800 m from the greenhouse site.
Distance from environmentally and otherwise protected areas	The nearest ecological site is 8 km to the northwest on the same ridge as the university.

4.1.3 A description of the environment immediately surrounding the release site

City environment with high buildings, paving, and streets. Trees and small flowerbeds are found at intervals along the streets.

4.1.4 The barriers planned to segregate the experiments constituting the trial release from the surrounding environment

Glass, netted air vents, treated water catchment, double-entry doors with an air lock.

4.1.5 The supervision and monitoring of the trial release

Senior staff and students undertake daily supervision and monitoring. The facility is kept locked.

4.1.6 The contingency plans to deal with extreme conditions such as storms, floods, and bushfires during the course of the trial release

Shadow netting protects against hail. The research facility has standard emergency facilities for fire and floods.

4.1.7 The provisions to remove or eliminate the GMO from the test site or any other place where it may be found upon completing the trial release and to restore the test site and any such other place to its status quo.

The soil, pots, and plants from the trial will be autoclaved and the room will be sterilized with an insecticide fogger.

4.1.8 The arrangements for producing the GMO in quantity

The sunflowers will be grown from seed.

4.1.9 The arrangements for transporting the GMO to the release site

The GM seed will be carried to the facility and potted in the greenhouse.

4.1.10 The quantity of the GMO to be released

Six GM plants will be used to pollinate six replicates of eight local wild relatives.

4.2 What potential hazardous or deleterious effects resulting from the trial release of the GMO can be postulated?

None. No sunflowers or related species are growing near the university greenhouse site, so an accidental release would have no effect.

4.3 Have similar releases of similar GMOs been made previously, either within or outside this country?

Yes. The university carried out efficacy greenhouse trials with the same GMO in the previous year.

4.4 What data are available to suggest that the introduced genetic trait has no deleterious effect in the long term upon the species into which it has been introduced or allied species or any other organisms or the environment in general?

No data are available to determine the long-term impact of this GM sunflower on other species. However, the modification is expected to have a positive benefit to the plant and a negative benefit to fungi in the sunflower fields. Whether the modification results in increased weediness of the crop will need to be assessed in field trials. These cannot be carried out until some data are available on the rate of gene spread to related species (this trial). The effect on fungal populations also will be assessed in future field trials, but this impact is expected to be less than the current treatment, which requires the application of broad-spectrum fungicides onto seeds, soil, and sometimes crops.

4.5 Is the GMO intended to modify the characteristics or abundance of other species? If so, what are these?

The modification is designed to lower the incidence of fungal species growing on the sunflower crop.

4.6 What experimental results or information exist to show the probable consequences (positive and negative) of the release of such a modified organism, including impacts on:

4.6.1 Human, animal, or plant health?

None.

4.6.2 Agricultural production?

Secure better yields and better quality of seed: laboratory data show that the proteins produced by the resveritol genes act as growth retardants to target pathogenic fungal species of sunflower crops.

4.6.3 Target and nontarget organisms in the area?

None.

4.6.4 The general ecology, environmental quality, and pollution in the area; and genetic resources (e.g., susceptibility of economically important species to herbicides, pesticides, etc.)?

None. This data will be collected in future trials if the efficacy of the GM sunflowers warrants commercial release.

4.7 Will the trial release have any unlikely but possible impacts?

None are anticipated.

4.8 What will be the consequences if the organism remains in the environment beyond the planned period?

The plants will be in containment facilities. The facility will be disinfected according to standard procedures at the end of the experiment.

4.9 Has a trial release been carried out in the country of origin of the GMO?

No.

5. Crop or Pasture Plants

5.1 Will the plants in this experiment be allowed to set seed?

Yes.

5.2 Is vegetative propagation planned?

No.

5.3 What desirable effects are expected to result from the use of the modified plant (e.g., increased production, improved quality of product, new product, disease, insect or herbicide resistance, etc.)?

If effective, the new modification is expected to provide improved protection against fungal infections, to reduce the use of chemical applications currently used to control these pathogens, and to produce better quality seed. The modification may have a positive effect on yields.

5.4 What undesirable effects may result from the release (e.g., reduced fertility, increased disease prevalence, production losses, etc.)?

No undesirable effects are expected. The crop will have an impact on populations of pathogenic fungi, but to a lesser extent than the current practice of applying chemical fungicides to seed, soil, and plants.

5.5 Are any of the likely gains directly linked to losses in other characteristics of the species?

No.

5.6 Are any members of the genus of modified plants known to be weeds?

Yes.

5.7 Can the genetic trait be transmitted by means other than by normal reproduction?

No. Although some evidence exists for very rare interspecies transfer of genes from plant pollen to microbes, the presence of this GMO is not expected to increase such transfer because the genes are already natural components of agricultural environments.

5.8 Does the imparted characteristic have the potential to add or subtract substances from the soil (e.g., nitrogen)?

No.

5.9 Has the modified plant been shown to be nontoxic to animals and humans?

Not yet.

5.10 Could any toxic products concentrate in the natural or human food chain?

Not known, but not expected because none of the new gene products are suspected toxins.

5.11 With regard to the pollination characteristics of the species, do wild populations of the species, or related species with which it can interbreed, exist in the vicinity of the field trial or agricultural site? If so:

No natural populations, but the area in a 100 m radius around the Life Sciences Building will be checked weekly for related species, and these will be removed immediately.

5.11.1 Have any experiments been conducted to test the phenotypic expression of the novel genetic material in the wild form or the related species?

These experiments will be carried out in future trials with seed collected from this experiment.

5.12 With regard to the pollination characteristics of the plant, what is the likelihood of the novel genetic material entering a pre-existing gene pool? Provide information on the pollinators specific to the crop and the measures to be taken to prevent pollen spread to unmodified plants.

This experiment is designed to provide the information to answer this question. Insect and manual pollination will be used to determine which local relatives of sunflower are sexually compatible with the crop through insect pollination or manual pollination. Net screens on the greenhouse vents and doors will prevent insects from entering or leaving the greenhouse. The greenhouse has a double-door entry system, and the vestibule will be sprayed with an insecticide before the outside door is opened. An insecticide spray will be used before and after the experiment to eliminate insects in the study area.

5.13 Should the imparted characteristic (e.g., insect, herbicide, or disease resistance) "escape" into a wild population, would it have the potential to affect the distribution and abundance of that population?

Unlikely. Escape of these genes is unlikely to result in transgenic seed production outside the contained study area. In the unlikely event that this should happen, the fungal tolerance and herbicide tolerance are not expected to give any fitness advantage to the new transgenics. For any fitness advantage to occur, the transgenics would need to be exposed to a high and ongoing level of fungal infection or herbicide application.

5.14 Would there be any consequent problems with respect to:

5.14.1 Agriculture?

None of the related wild species are weeds in agricultural areas.

5.14.2 The environment?

Not yet known.

5.14.3 Disease control?

Not yet known.

5.15 If there is any possibility of 5.12 and/or 5.13 occurring, has any attempt been made to minimize the risk (e.g., by imparting male sterility)?

Male sterility is available in this crop, but data still will be needed on sexually compatible local relatives. Cytoplasmic sterility will be used if hazards are identified. Breeders use restoration genes to overcome cytoplasmic male sterility during crossing.

5.16 Could the imparted characteristic (either in the cultivated population or in a wild population) provoke a genetic response in populations of other species (e.g., increase the resistance of an insect population to an insecticide)?

Unlikely. But this can be further studied in future field trials.

CASE STUDY 3: Application for Field Trials with Genetically Modified Bananas Containing a Vaccine against Hepatitis B

1. Brief Description of Proposed Trial Release

The major epitope protein of the Hepatitis B virus has been cloned into banana to enable an effective vaccine delivery system to children and adults in developing countries. It is necessary to compare the suitability of eight banana clones to your country's climatic conditions. These trials will examine two parameters relevant to potential adoption and use: (1) growth rates of newly propagated and five-year-old plants, and (2) level of gene expression in the fruit.

2. Objective

2.1 What is the aim of the proposed trial release of the genetically modified organism (GMO)? What are the benefits of this approach compared with other possible methods, especially those not involving planned release?

The current vaccine for Hepatitis B is the same cloned viral protein, but delivery is in a pharmacological package designed for injection. Storage and hygiene of injected vaccines have been problematic in rural areas of developing countries where refrigeration and supplies are not readily available. In addition, injections cause significant trauma to children and adults. Packaging the vaccine protein in an edible fruit is a convenient, cost-effective, and humane way of ensuring that adequate doses are delivered to all people in high-risk areas.

2.2 If the trial release is successful, do you intend to propose a general release of the GMO?

Yes

If so:

2.2.1 When do you propose that the general release would take place?

Once medical clearance is obtained—approximately three years.

2.2.2 Where do you propose that the general release would take place?

Worldwide in banana growing areas.

2.2.3 By whom do you propose that the GMO would be released?

An international health organization.

2.3 Do you intend to market the GMO as a product in this country?

Yes.

3. Nature of Organism and Novel Genetic Material

3.1 What is the species of GMO to be released?

Banana plants (*Musa* spp.).

3.2 Do the unmodified form(s) have any adverse effect on:

3.2.1 Humans, animals, or plants?

No.

3.2.2 Agricultural production?

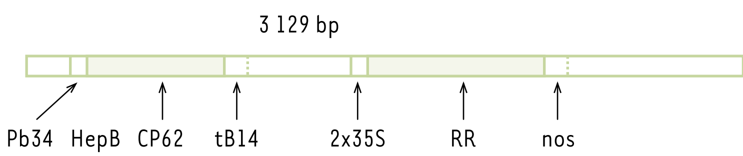
No.

3.2.3 Any other aspect of the environment?

No.

3.3 Furnish a description of the genetic, and resultant phenotypic, modifications of the GMO. This should include the origin of the inserted DNA, the procedure used to induce the genetic modification, and the extent to which it has been characterized.

The Hepatitis B vaccine protein was cloned from the virus and inserted into a plasmid containing a tissue-specific promoter that only expresses the protein banana fruit. The plasmid also contains an herbicide-resistance marker gene. The plasmid was shot into banana tissue using a helium gun. Plantlets were regenerated from transformed cells of eight banana varieties. Stable transformants were selected over ten generations of plants regenerated in tissue culture.



Linear DNA fragment inserted into banana

KEY

Pb34 = fruit specific promoter from tomato
HepB CP62 =major epitope coat protein from Hepatitis B virus strain 4589
tB14 = terminator from tomato polygalacturonase gene
2x35S = two copies of the CaMV 35S promoter
RR = glyphosate herbicide tolerance gene
nos = nopaline synthase terminator from *Agrobacterium*

3.4 What is the frequency of reversion, i.e., loss of genetic modification?

None.

3.5 How do you verify that you have the desired GMO?

Hybridization and herbicide tolerance.

3.6 What methods will you use to test for batch-to-batch consistency?

Elisa testing.

3.7 What is the expected survival time of the GMO under conditions likely to be found in the proposed release area(s) and surrounding environment(s)?

The plants will survive for three to ten years in cultivated fields.

3.8 Describe normal dispersal mechanisms of the species and characterize the capability of the GMO to disperse from the release area.

Bananas are cultivated vegetatively. New stock is obtained through tissue culture to optimize virus disease control in the crop.

3.9 If, at any stage in the future, biosafety regulators need to ascertain whether the GMO in a field is the same as that specified here, what means are available?

Hybridization and herbicide tolerance.

3.10 Provide a protocol and materials to enable detection of foreign gene(s) in surrounding microbial, plant, or animal life.

Protocols attached.

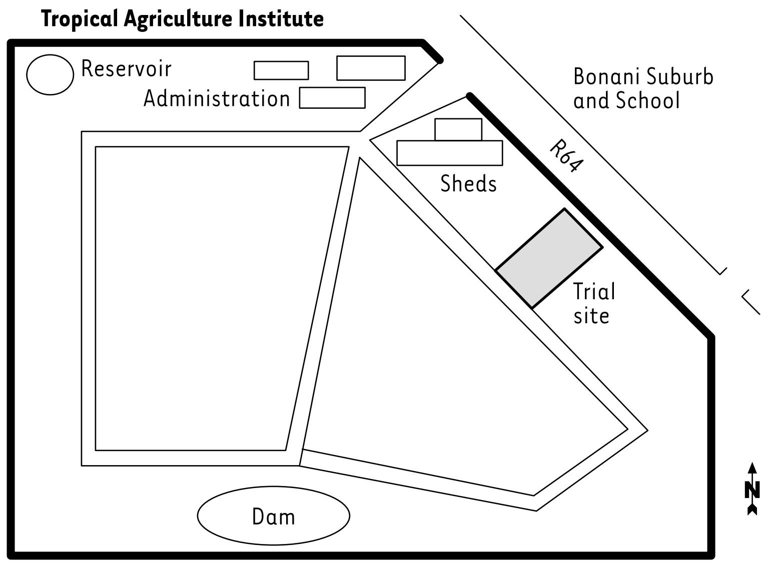
4. Trial Release: General

4.1 Full details are required about the manner in which the trial release of the GMO is to be undertaken.

The bananas will be planted at the Tropical Agriculture Institute's research facility, which is surrounded by a fence to minimize pilfering. Access to the trial site will require a key and will be by authorized personnel only. A sign on the fence will have a skull and crossbones and say, "Test bananas, not for human consumption."

The trial site is within the grounds of the institute, on a southwest slope. Water drains from the site to the dam. The institute is surrounded by subtropical vegetation to the north, west, south and by a suburb on the east. The R64 road separates the institute from the suburb. The site will have no bordering banana plantings. About 42 clones of each of the 8 transformed varieties will be planted. Plants that die or fail to grow will be replaced by seedlings from the lab stocks. The trial site will be fenced with a 2-meter-high mesh fence and locked with an access gate. Fruit from the plants will be collected and moved to the laboratory for further testing.

The trial will run for three years and will be supervised at all times by trained personnel. A flood



would, at the very worst, wash the plants down to the dam, but this is highly unlikely because no such floods have been recorded in the area.

After the trial the plants will be removed and burnt.

4.2 What potential hazardous or deleterious effects resulting from the trial release of the GMO can be postulated?

The vaccine bananas are not toxic even when consumed at a high rate.

4.3 Have similar releases of similar GMOs been made previously, either within or outside the country?

No.

4.4 Have similar requests or applications for the release of this particular GMO been made previously?

No.

4.5 Is there any evidence that the inserted genetic trait is transferable to other organisms in the release site and surrounding environment?

The banana flowers are mostly sterile, but will be bagged to prevent pollen release into the environment.

4.6 What data are available to suggest that the introduced genetic trait has no deleterious effect in the long term upon the species into which it has been introduced or allied species or any other organisms or the environment in general?

The Hepatitis B epitope protein is being used already as a vaccine, and its lack of toxicity was established before it was approved for medical use.

4.7 Is the GMO intended to modify the characteristics or abundance of other species?

No.

4.8 What experimental results or information exist to show the probable consequences (positive and negative) of the release of such a modified organism, including impacts on:

4.8.1 Human, animal, or plant health?

The protein will increase resistance to Hepatitis B in consumers able to invoke an immune response.

4.8.2 Agricultural production?

None.

4.8.3 Target and nontarget organisms in the area?

None.

4.8.4 The general ecology, environmental quality, and pollution in the area?

None.

4.8.5 The genetic resources (e.g., susceptibility of economically important species to herbicides, pesticides, etc.)?

None.

4.9 Will the trial release have any unlikely but possible impacts?

No.

4.10 What will be the consequences if the organism remains in the environment beyond the planned period?

None.

4.11 Has a trial release been carried out in the country of origin of the GMO?

No.

4.12 Provide a draft copy of a press release informing the public of the trial or general release of the GMO.

Attached.

5. Trial Release: Vaccines

5.1 For human clinical trials, what arrangements are proposed to dispose of waste containing any vaccine organisms?

Clinical trials are not part of this application. They are already under way in Europe.

5.2 Will the subjects carry live vaccine organisms at the end of the trial? If so:

5.2.1 Will they be likely to disseminate the live vaccine organisms to the general population?

N/A

5.3 On the basis of data obtained in contained experiments (please supply), what effects are expected when the vaccine organism interacts with target and nontarget species in the test area and surrounding environment?

N/A

5.4 What is the existing evidence regarding level and duration of immunity produced in the target species?

These data are being collected.

5.5 What challenge or other tests using virulent field strains are to be carried out on vaccinated animals?

N/A

5.6 Is there likelihood that the host vaccine organism would be used in other human or animal vaccines?

Yes.

5.7 Would the use of this vaccine preclude the future use of the host vaccine organism for immunization purposes?

No.

6. Crop or Pasture Plants

6.1 Will the plants in this experiment be allowed to set seed?

No.

6.2 Is vegetative propagation planned?

No.

6.3 What desirable effects are expected to result from the use of the modified plant (e.g., increased production, improved quality of product, new product, disease, insect or herbicide resistance, etc.)?

Improved vaccine delivery system for tropical and subtropical developing countries.

6.4 What undesirable effects may result from the release (e.g., reduced fertility, increased disease prevalence, production losses, etc.)?

None.

6.5 Are any of the likely gains directly linked to losses in other characteristics of the species?

No.

6.6 Are any members of the genus of modified plants known to be weeds?

No.

6.7 Can the genetic trait be transmitted by means other than by normal reproduction?

No.

6.8 Does the imparted characteristic have the potential to add or subtract substances from the soil (e.g., nitrogen)?

No.

6.9 Has the modified plant been shown to be nontoxic to animals and humans?

Yes.

6.10 Could any toxic products concentrate in the natural or human food chain?

No.

6.11 With regard to the pollination characteristics of the species, do wild populations of the species, or related species with which it can interbreed, exist in the vicinity of the field trial or agricultural site?

No.

6.12 With regard to the pollination characteristics of the plant, is it likely that the novel genetic material will enter a pre-existing gene pool? Provide information on the pollinators specific to the crop and the measures to be taken to prevent pollen spread to unmodified plants.

No. The flowers are mostly sterile, but will be bagged at the onset of flower development and kept bagged until harvest.

6.13 Should the imparted characteristic (e.g., insect, herbicide, or disease resistance) "escape" into a wild population, would it have the potential to affect the distribution and abundance of that population?

No.

6.14 Would there be any consequent problems with respect to:

6.14.1 Agriculture?

No.

6.14.2 The environment?

No.

6.14.3 Disease control?

The GM crop is designed to combat viral disease in humans.

6.15 If there is any possibility of 6.12 and/or 6.13 occurring, has any attempt been made to minimize the risk (e.g., by imparting male sterility)?

No.

6.16 Could the imparted characteristic (either in the cultivated population or in a wild population) provoke a genetic response in populations of other species (e.g., increase the resistance of an insect population to an insecticide)?

No.

CASE STUDY 4: Application for Field Trials with Cotton Genetically Modified for Increased Resistance to Insect Attack

1. Brief Description of Proposed Trial Release

It is proposed to run field trials with three transgenic cotton varieties that contain a bacterial gene for an insect toxin. The trials will use comparisons between fields (1) seeded with the three local bollworm pests, (2) open to natural infection and untreated, (3) open to natural infection and given standard insecticide treatments. Comparisons will be made with conventional varieties for each treatment.

2. Objective

2.1 What is the aim of the proposed trial release of the genetically modified organism (GMO)? What are the benefits of this approach compared with other possible methods, especially those not involving planned release?

Bollworm infections cause severe damage to cotton crops in the region. The level of damage varies from year to year depending on environmental conditions. After hatching, the larvae move quickly into the bolls, where they are protected from insecticide sprays. This does not stop farmers from trying to control insect infections using vast quantities of insecticide. Introducing the Bt toxin into the plant itself affects only feeding insect larvae and targets the pests as they begin to feed on the crop. The toxin is completely safe for all other non-Lepidopteran animals including humans. Bt cotton has the potential to provide effective bollworm control and is a much more environmentally friendly farming method.

2.2 If the trial is successful, do you intend to propose a general release of the GMO?

Yes.

2.2.1 When do you propose that the general release would take place?

About five years.

2.2.2 Where do you propose that the general release would take place?

In the rural cotton-growing areas.

2.2.3 By whom do you propose that the GMO would be released?

Local cotton industry.

3. Nature of Organism and Novel Genetic Material

3.1 What is the species of the GMO to be released?

Three commercial varieties of *Gossypium* sp.: NAM450, SA366, QEU890.

3.2 Do the unmodified form(s) have any adverse effect on:

3.2.1 Humans, animals, or plants?

None.

3.2.2 Agricultural production?

None.

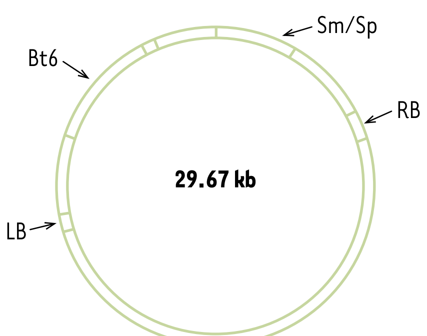
3.2.3 Any other aspect of the environment?

None.

3.3 Furnish a description of the genetic, and resultant phenotypic, modifications of the GMO. This should include the origin of the inserted DNA, the procedure used to induce the genetic modification, and the extent to which it has been characterized.

The cotton varieties contain a Cry1A Bt toxin isolated from the common soil bacterium *Bacillus thuringiensis*. Bt toxins are known for their very narrow host range, and different toxins target different insect species. The toxin lies behind a CaMV S35 promoter that expresses the toxin at low levels (< 14 ng/g dry weight) in all plant tissues. This is enough to kill one- to three-instar larvae, but will not harm older larvae. In addition to the Bt gene, there is an antibiotic marker gene coding for resistance to streptomycin and spectinomycin. This gene lies behind a bacterial promoter that is not operational in plant tissues.

Map of the disarmed Ti-plasmid used to transform cotton



KEY

LB-RB = T-DNA transferred into cotton (4,38 kb)

Bt6 = cry1A from *Bacillus thuringiensis* modified for plant codon usage; 35S promoter and nos terminator

Sm/Sp = spectinomycin and streptomycin resistance gene from *Streptomyces* soil isolate; bacterial promoter and 2x nos terminator

3.4 What is the frequency of reversion, i.e., loss of genetic modification?

None observed.

3.5 How do you verify that you have the desired GMO?

Hybridization and bioassays.

3.6 What methods will you use test for batch-to-batch consistency?

Hybridization.

3.7 On the basis of contained experiments, indicate:

3.7.1 The survival rates of the GMO in the spectrum of conditions that are likely to be found in the proposed release area(s) and surrounding environment(s)

Cotton is a cultivated crop propagated by seed. Because very few volunteer or escaping cotton plants have been observed in cotton-growing areas, it is unlikely that the crop will disperse from the growing area. The plant is most likely to be spread by farmers wishing to cultivate it in new areas.

3.7.2 The capability of the GMO to disperse from the release area and the dispersal mechanisms

It is unlikely that seed will be dispersed from the growing area by birds or other animals. It will, however, be necessary to prevent opportunistic harvest of seed by farmers.

3.7.3 Any other relevant information

3.8 If, at any stage in the future, biosafety regulators need to ascertain whether the GMO is the same as the GMO specified here, what means are available?

Hybridization.

3.9 Provide a protocol and materials to enable detection of foreign gene(s) in surrounding microbial, plant, or animal life.

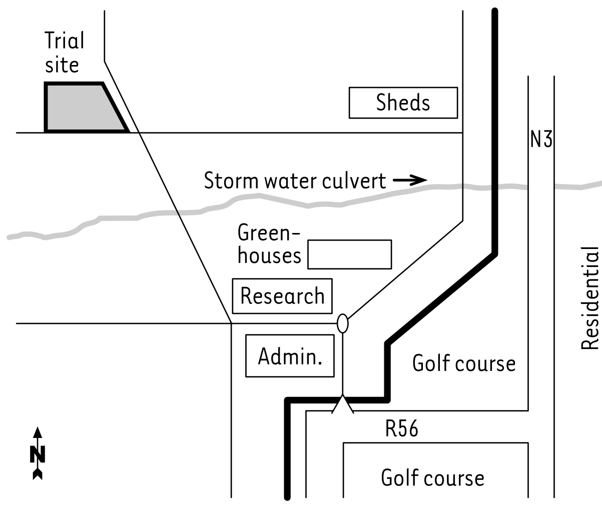
Attached.

4. Trial Release: General

4.1 Full details are required about the manner in which the trial release of the GMO is to be undertaken.

The trial site is inside the Northern Agricultural Research Unit property. It lies on a south-facing slope and is far away from any general access area or public pathway. The trial site is surrounded by other crop trials on all sides. The closest other cotton planting will be 800 m south of the GM trial site.

The site is about 0.6 km from the nearest habitation to the east and 200 m from a storm water culvert to the south. The closest natural area is 10 km to the west. Trained personnel will monitor the trial. Should a disaster happen such as a flood, it is unlikely to uproot and move the cotton. Seed will be planted in October.



4.2 What potential hazardous or deleterious effects resulting from the trial release of the GMO can be postulated?

None.

4.3 Have similar releases of similar GMOs been made before, either within or outside this country?

Yes.

If so:

4.3.1 What were the beneficial consequences?

Commercial plantings of Bt cotton are already approved in neighbouring countries, and trials in dry-land rural areas have shown marked benefit to small and resource-poor farmers.

4.3.2 What were the adverse consequences?

None.

4.3.3 What factors might suggest a greater, or a lesser, risk for adverse consequences for the now-proposed trial release?

None.

4.4 Have similar requests or applications for the release of this particular GMO been made previously?

No.

4.5 Is there any evidence that the inserted genetic trait is transferable to other organisms in the release site and surrounding environment?

The foreign genes are only transferable to sexually compatible plants in the region around the trial. Pollen is transferred by insects, mainly bees. The GM cotton is 800 m from the closest conventional cotton planting. There is no evidence of closely related plant species in the local flora.

4.6 What data are available to suggest that the introduced genetic trait has no deleterious effect in the long term upon the species into which it has been introduced or allied species or any other organisms or the environment in general?

Bt cotton is being grown in six countries worldwide where it is being closely monitored for development of resistance in target populations. After three years, no sign of resistance has been found in or around commercial cotton fields.

4.7 Is the GMO intended to modify the characteristics or abundance of other species?

The transgenic cotton varieties are designed to reduce the number of bollworms in cotton plantations. Part of this study will be an examination of insect populations in and around the trial site and after certain insecticide treatments.

4.8 What experimental results or information exist to show the probable consequences (positive and negative) of the release of such a modified organism, including impacts on:

4.8.1 Human, animal, or plant health?

Existing crops using Bt technology have proved completely safe for human consumption and to have no impact on nontarget insects or other animals in the food web.

4.8.2 Agricultural production?

Insect tolerance in cotton will enable better yields, decreased use of insecticides, improved production, and better quality of cotton.

4.8.3 Target and nontarget organisms in the area?

While bollworm populations may decrease in Bt cotton fields, the natural populations of bollworm will probably be little affected because these insects have alternative hosts in the wild.

4.8.4 General ecology, environmental quality, and pollution in the area?

Inserting Bt insecticides in crops will reduce the impact that insecticides have on the full range of insects in any commercial farming community. Experience with Bt cotton has shown that the fields return to an active ecosystem in the absence of broad-spectrum insecticides. Nontarget insects and birds become abundant in Bt cotton fields.

4.8.5 Genetic resources (e.g., susceptibility of economically important species to herbicides, pesticides, etc.)?

Bt is unlikely to affect genetic resources in the area because the only insects that are affected are lepidopterans that eat parts of the plant. The poor natural germination of cotton seed and the absence of wild relatives will ensure that the genetic modification has no negative impact on the environment.

4.9 Will the trial release have any unlikely but possible impacts?

No.

4.10 What will be the consequences if the organism remains in the environment beyond the planned period?

None.

4.11 Has a trial release been carried out in the country of origin of the GMO?

No.

4.12 Provide a draft copy of a press release informing the public of the trial or general release of the GMO.

Attached.

5. Crop or Pasture Plants

5.1 Will the plants in this experiment be allowed to set seed?

Yes.

5.2 Is vegetative propagation planned?

No.

5.3 What desirable effects are expected to result from the use of the modified plant (e.g., increased production, improved quality of product, new product, disease, insect or herbicide resistance, etc.)?

The insect-tolerant cotton will enable farmers to control bollworm infections without need for environmentally unfriendly, broad-spectrum insecticides.

5.4 What undesirable effects may result from the release (e.g., reduced fertility, increased disease prevalence, production losses, etc.)?

The yield and quality of cotton should increase and the amount of insecticide used should decrease.

5.5 Are any of the likely gains directly linked to losses in other characteristics of the species?

No.

5.6 Are any members of the genus of modified plants known to be weeds?

No.

5.7 Can the genetic trait be transmitted by means other than by normal reproduction?

No.

5.8 Does the imparted characteristic have the potential to add or subtract substances from the soil (e.g., nitrogen)?

No. Bt protein is rapidly degraded in the soil and in sunlight.

5.9 Has the modified plant been shown to be nontoxic to animals and humans?

Yes. The foreign proteins are nontoxic to humans and all animals except certain Lepidopteran insects. Bt toxin is the insecticide of choice in organic farming systems.

5.10 Could any toxic products concentrate in the natural or human food chain?

No. The toxin breaks down along with other cellular proteins in rotting plant material.

5.11 With regard to the pollination characteristics of the species, do wild populations of the species, or related species with which it can interbreed, exist in the vicinity of the field trial or agricultural site?

No related plants have been identified in local flora or weed species, so out-crossing is not expected to occur.

5.12 With regard to the pollination characteristics of the plant, what is the likelihood of the novel genetic material entering a pre-existing gene pool? Provide information on the pollinators specific to the crop and the measures to be taken to prevent pollen spread to unmodified plants.

Because cotton is pollinated by insects, the trial site is situated 800 m from the nearest cotton, and insect traps will be used to collect insects moving away from the GM trial site. These insects will be monitored to obtain data on GM pollen movement from the GM cotton.

5.13 Should the imparted characteristic (e.g., insect, herbicide, or disease resistance) "escape" into a wild population, would it have the potential to affect the distribution and abundance of that population?

No.

5.14 Would there be any consequent problems with respect to:

5.14.1 Agriculture?

No.

5.14.2 The environment?

No.

5.14.3 Disease control?

No.

5.15 If there is any possibility of 5.12 and/or 5.13 occurring, has any attempt been made to minimize the risk (e.g., by imparting male sterility)?

Not necessary.

5.16 Could the imparted characteristic (either in the cultivated population or in a wild population) provoke a genetic response in populations of other species (e.g., increase the resistance of an insect population to an insecticide)?

Possibly. Insect resistance is a factor in the development of any insecticide, not just GM insecticides. No resistance has been detected to Bt cotton crops, but this may be a result of stringent resistance-management systems in place wherever Bt cotton is grown in the world. Should the crop be commercialized in this country, insect-management strategies would also be introduced here.

CASE STUDY 5: Application for Commercial Release of Genetically Modified Herbicide-Tolerant Soya

1. Brief Description of the Genetically Modified Plant

The transformed soya varieties (*Glycine max*) are all suited to local production. They have been transformed with a *Gox* gene from the soil bacterium *Streptomyces*. This gene confers resistance to the herbicide, Roundup. Herbicide tolerance offers a significant benefit for farmers, consumers, and the environment. This technology allows the farmer to use fewer agrochemical applications, to plough less, to use less fuel, and to produce a product with lower chemical residues.

2. General Release

The seed will be marketed to farmers through existing channels. The bags and brochures will be clearly labeled "genetically modified," and information about the modification will be provided to all seed buyers. Information will also be provided on the revised growing strategies and how to make the very best use of the technology. Farmers will be encouraged to declare the harvest as genetically modified at oil seed depots. The first crop is expected in two years. The first year will be used to bulk up seed for sales in the second year. The second-year crop will make up about 10% of the total soya production. This is expected to increase to 80% over five years, with 20% kept GM-free to exploit European niche markets and their inflated prices.

3. Description of Any Product Derived from the Plant

Soya is used in about 1,600 processed food products as a filler and as a source of healthy, affordable protein. Processing and cooking denatures the foreign DNA and foreign gene product. In the absence of local labeling guidelines for GM foods, food processors have been asked to label all foods containing detectable foreign protein as "genetically modified." This will probably require the labeling of milled, unprocessed soya meal, but no other products in the processing line. Soya seed is exported to neighboring countries and will be declared "GM" before shipment.

4. Brief Summary of Field Trials Undertaken

Six years of field trials have been undertaken in this country. The trial data have shown that gene transfer to local flora does not occur and have supported the claim that the herbicide-tolerant soy leads to increased production, decreased herbicide usage, decreased plant damage, and decreased soil erosion through the associated conservation tillage techniques.

Table 1 shows results obtained in comparative trials with four GM soya varieties in three growing areas. In each area the suitable GM soya varieties were compared to the best available conventional variety for that area. These data are the average of results over two growing seasons.

Table 1: Data collect from comparative trials during two growing seasons

	PERCENTAGE DIFFERENCE COMPARED TO BEST CONVENTIONAL VARIETY FOR THE GROWING AREA				AVERAGE % FOR THREE GROWING AREAS
PARAMETER	VAR1	VAR2	VAR3	VAR4	
Herbicide used	−23	−34	−21	−19	−24.25
Soil erosion	−63	−57	−71	−58	−62.25
Plant damage	−9	−6	−11	−13	−9.75
Yield	12	9	11	9	+10.25

5. Pollen Spread

Pollination in soya occurs before the flower opens, and remaining pollen is largely infertile by the time the flower opens and is visited by bees and other insects. The pollen has proved nontoxic to seven local pollinating species known to visit soya fields. No cross-pollination was observed to related weed species, and no indigenous relatives of soya occur in this country.

6. Seed Dispersal

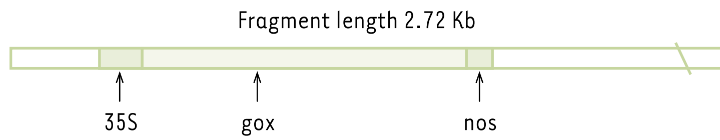
The marketed seed will be labeled as "genetically modified" and all growers will receive information on the technology and how to implement revised herbicide treatment and conservation tillage procedures. The plant is spread by seed dispersal and the seeds are viable. However, studies around soya fields show that there is little dispersal beyond the planted area and no evidence of roadside volunteers could be found. Soya is also controlled by three other registered herbicides in this country, enabling volunteers to be controlled chemically or by tillage. Should GM soya escape into natural areas (no evidence of this has been observed with unmodified crops), it will have no selective advantage, because herbicides are not used in these areas. No adverse affect on the environment is expected.

7. Vegetative Spread of the Genetically Modified Plants

Soya is not spread vegetatively.

8. Foreign Genes and Gene Products

The soya varieties all contain the same gene construct. The *Gox* gene is from *Streptomyces* and codes for a single protein that inactivates the active compound in glyphosate herbicides. The protein lies behind a CAMV 35S promoter that expresses the gene in all plant tissues at all growth stages. Foreign protein levels in seed are between 8 to 20 ng per g dry weight. This is very low and is undetectable under some growing conditions. The DNA and the protein from the *Gox* gene are quickly digested in animal digestive juices (10 to 15 seconds) and are rapidly degraded during the heat and shearing processing methods used to produce processed food additives (Table 2). The genes have been stable for 12 growing seasons.



Linear DNA fragment transformed into soya to give RR resistance

KEY

P35S = CaMV promoter
gox = herbicide-tolerant gene from *Streptomyces* sp.
nos = nopaline synthase terminator from *Agrobacterium* sp.
\ = a second insert (93bp) has been detected in RR soya, but has no coding region, produces no protein, and does not alter plant physiology in any detectable manner

Table 2: Quantitative PCR determinations of GM DNA as a percentage of soya food products

PRODUCT	NEGATIVE*	< 0.5%	0.5% < x < 2%	> 2%
Soya flour	0	0	17.9	82.1
Soya grist	0	8.75	74.0	17.25
Soya protein	0	10.0	87.5	2.5
Composed food	92.0	8.0	0	0

A comparative study by 16 Swiss analytical laboratories averaging the data for two primers: RR and 35S (Nat/Biotech 17:1137–1138, 1999)
* All negative controls were correctly detected by all laboratories.

10. Resistance

No resistance developed to the herbicide tolerance gene in the first 12 growing seasons. However, some recent reports suggest that 6 years of intensive use over large acreage may lead to the development of resistance in some weeds. Should this be the case (it is currently being investigated), the use of alternative herbicides at certain intervals will correct the problem.

11. Human and Animal Health

The *Gox* protein has been tested in human and animal health trials by three independent teams. No evidence of toxicity or allergenicity has been found. A nationwide French study in 1998, to investigate increasing reports of allergenicity to soya, found that the increase correlated with increased consumption of soya and improved allergenicity testing procedures, not with the advent of GM soya as had been hypothesized. The researchers reported that GM soya is the only soya that is tested for allergenicity.

12. Environmental Impact and Protection

Soya has been grown in this country for 15 years with no adverse impact on the environment. Soya is neither weedy nor invasive. The GM soya is not going to change this pattern. GM soya is no more likely to escape into the environment than conventional soya varieties. Any selective advantage conferred on GM soya by the Gox gene is only effective when the Roundup Ready herbicide is used. Thus, the selective advantage is confined to agricultural areas and can be quickly reversed by other herbicides and mechanical treatment. Roundup Ready soya has been shown to be safe for consumption and to have significant environmental benefits including a decrease in soil erosion, input costs, and herbicide usage.

13. Socio-Economic Impact

Soya is mainly grown by commercial farmers in this country. No adverse socio-economic impact is expected. On the contrary, the GM soya will enable commercial farmers to produce soya more competitively, with less environmental impact, and to produce better quality crops.

14. Waste Disposal

The plant waste associated with the harvest of soya will be used in animal fodder, as is that associated with unmodified soya.

CASE STUDY 6: Application for Commodity Imports of Genetically Modified Maize

1. Brief Description of the Genetically Modified Plant

This application is for the import of genetically modified maize for food processing, *not planting.* A shortage of yellow maize is being experienced, and it will be necessary to import maize from the United States and Argentina. Because as much as 50% or more of maize crops in these countries is genetically modified, it must be assumed that imports will contain some GM seed.

2. General Release

These imports will not be used for planting, but only for food and feed processing. The seed will be milled and is not expected to escape into the local environment. We propose to import the commodity maize using the conditions devised for phytosanitary containment. The seed will be offloaded into sealed containers, shipped to the nearest mill, and milled immediately. No storage of seed will be allowed. The milled maize is nonliving and will not grow and reproduce when released into the food chain.

3. Description of Any Product Derived from the Plant

The seed will be used to produce maize products for the food industry (glucose syrups, etc.) and animal feeds. Milled maize will be declared "genetically modified" when purchased from the mills. The importers have no control over labeling beyond this point.

4. Brief Summary of Field Trials Undertaken

It is not clear which modifications will be in the seed imports, but all have received human and animal health safety permits in the country of origin. Product development would have required a number of years of trials in the country of export. A summary of the food and feed safety data for all the possible events in imports is given in the attached table.

Summary of food safety data for maize transformations approved in exporting countries

EVENT	NEW TRAIT	TOXICITY	PATHOGENICITY	DIGESTIBILITY	ALLERGENICITY	LEVEL IN GRAIN*	MARKER GENE	NUTRITION & COMPOSITION CHANGES**	EXISTING APPROVALS
GV 367	Insect tolerance Bt cry1A	None	None	8–10 sec	None	8 ng/g	Kanamycin antibiotic resistance	No statistically significant differences	Food and feed use: EU, USA, Canada, Argentina
MOL 3T6	Insect & herbicide tolerance Bt cry1AB + EPSPS	None	None	8–11 sec	None	20 ng/g	Glyphosate (herbicide) tolerance	No statistically significant differences	Food and feed use: USA, Argentina
AG Novo	Insect tolerance Bt cry9c	None	None	18–20 sec	No similarity, but slow digestion	14 ng/g	Streptomycin/ Spectinomycin antibiotic resistance	No statistically significant differences	Food and feed use: USA, Argentina
PILT 56	Insect & herbicide tolerance Bt cry1A + bar	None	None	6–12 sec	None	38 ng/g	Phosphinothricin (herbicide) tolerance	No statistically significant differences	Feed use: USA

NOTE: These are fictitious data and do not represent any known GM events. *Foreign protein; dry weight **Comparison with nontransformed equivalent variety

5. Pollen Spread

Not applicable because the seed will not be planted.

6. Seed Dispersal

Using phytosanitary containment conditions (sealed containers), the seed is unlikely to drop off trucks during transport from harbors to mills.

7. Vegetative Spread of the Genetically Modified Plants

Maize does not spread vegetatively.

8. Foreign Genes and Gene Products

It is not clear which foreign constructs will be present in the imported seed. A list of approved maize transgenics is supplied for the United States, but no such list was available from Argentina.

9. Resistance

Resistance will not be an issue because the seed will be milled within 48 hours of landing and will not be allowed to grow in the country.

10. Human and Animal Health

All transgenic events in Argentina and the United States have passed human- and animal-safety assessments. It can be assumed that the seed will not pose a health risk to local consumers. Nonetheless, data have been supplied to enable an assessment by local health and nutrition experts. A summary of these data is given in the attached table.

11. Environmental Impact and Protection

Because the seed will not be planted, no environmental impact is expected.

12. Socio-Economic Impact

A shortage of maize puts tremendous stress on the price of this staple food. This has an adverse impact on the majority of the people in the country for whom maize is a staple source of nutrition and sustenance. Obtaining import contracts when prices are good enables local producers to source yellow maize for feed and food processing. This leaves locally grown white maize predominantly for food.

13. Waste Disposal

No waste disposal issues are raised with this general release because living GMOs will not be released into the environment and the plant material is not toxic.

Supplemental Crop Information

Sunflower as a Crop

Sunflower, *Helianthus annuus* Linnaeus, is an annual row crop that is grown primarily for its edible oil. Other uses and byproducts include animal feed, human snacks, and various chemical and industrial products.

The crop, and indeed the entire genus *Helianthus*, was unknown in the Old World until after Columbus. But it was grown by North American Indians for millennia throughout much of the United States and portions of Canada and Mexico. Sunflower subsequently spread to Europe for garden and oil use, and finally to Russia in the eighteenth century, where its use as an oil crop developed seriously. Reintroduction as a commercial crop in North America probably occurred in the latter nineteenth century. Commercial interest in North America and other parts of the world has increased throughout the current century.

Taxonomy of Sunflower

Sunflower belongs to the genus *Helianthus*, a genus of 67 species, all native to the Americas. The genus consists of both annual and perennials; some, such as *H. annuus*, are very common; some, such as *H. niveus* (Bentham) Brandegee, are quite rare; some are very weedy; and some are grown as ornamentals. In addition to the sunflower, the Jerusalem artichoke, *H. tuberosus* Linnaeus, is grown for food. Taxonomists have repeatedly noted that the distinctiveness of the genus within the Asteraceae (Compositae),is matched by the indistinctness of the species within the genus. This is perhaps caused by the variability within each species, natural interspecific hybridization, and various polyploid states of the native species.

Reproduction of Sunflower

Flowers are borne on a fairly standard Asteraceae capitulum of 700–8,000 individual florets. Disk flowers are perfect; ray flowers are sterile with a rudimentary pistil. Disk flowers within a single capitultum open centripetally for a period of 5–10 days or more; each capitulum may have, depending on timing, a central portion of unopened buds, surrounded by a ring of florets with exposed stamens, another ring of florets with exposed stigmas, and finally a ring of pollinated florets. On the morning of anthesis of an individual floret, the stamens elongate and shed pollen inward. Later that day, the style elongates and by the following morning presents a receptive stigma above the stamens with pollen brushed upward by stigma hairs. At this stage pollination of the stigma occurs. Removal of fertile flower parts at various stages, insect pollination, self-incompatibility, and male sterility alter the above pollination outline and can be used in breeding programs. Pollen can be moved physically from one flower to another, but movement of the large spiny grains by wind cannot occur farther than a few feet.

Traditional cultivars have been maintained as open pollinating populations, but more recent breeding approaches have involved hybrids dependent on male sterility/restorer systems introduced from wild *Helianthus* species.

Pollination of Sunflower

Honey bees are the primary pollinators of sunflower. Bumble bees, wild bees, and other insects may also be pollinators. Wind pollination is negligible. Without adequate numbers of pollinating insects, yield of sunflower may be low. Movement of sunflower pollen to other cultivated, wild, or weedy sunflower by bees can occur over considerable distance. Certified seed distance is 2,640 feet, and is increased to 5,280 feet between seed fields and wild or volunteer sunflower plants.

Crossability of Sunflower

Cultivated sunflower crosses readily with wild and weedy forms of *H. annuus*, which are common in many areas. Insect-aided pollination is the predominant method by which a high degree of cross-pollination takes place in sunflowers. Cultivated sunflowers are potentially capable of crossing with many other species of *Helianthus*, and naturally occurring hybrid swarms are known in North America. Interspecific hybridization involving *H. annuus* as one of the parents has been conducted for many years as part of breeding programs and taxonomic research. Hybridization ranges from easy and generally fertile crosses, such as with many of the other annual species, to high levels of incompatibility.

Weediness of Sunflower

The Asteraceae are one of the premier weed families. Sunflower follows the family pattern well. Aside from its value as a crop, sunflower is a common and difficult weed of cultivated land and disturbed areas. It is a common volunteer in field crops, developed from stray seed of the previous season. Any genetic alteration that would increase weedy tendencies or make control difficult would be a cause for concern to agriculture.

Seed Dispersal in Sunflower

The subject of seed dispersal inevitably leads to birds. For several reasons, sunflower seed is very attractive to many birds. The seeds have high levels of protein and fat that are useful to growth, molt, fat storage, and energy needs of birds. The seeds mature during the postbreeding season of most birds, when their energy demands are greatest. In some parts of the world, birds have many years of co-evolution with sunflower. Although most of the seed is consumed by the birds and becomes nonviable, an inevitable fraction is moved but not consumed. A certain percentage of seed always falls to the ground before and during harvest of commercial sunflower fields. This frequently results in volunteer plants in the next season.

Modes of Gene Movement

Genes may move out of the test areas by pollen or by seed. Because insect-vectored sunflower pollen may readily transfer genes to wild, weedy, or cultivated *H. annuus*, or other *Helianthus* spp. outside test areas, some means, such as flower removal, caging, etc., must be used to prevent such movement. Spatial isolation may not be realistic for some test sites. Seeds may serve as a means of movement either by bird dissemination, or simply by falling to the ground. Some means, almost certainly physical, must be implemented to prevent seed from falling and to prevent birds from taking seed.

Cotton as a Crop

Four species of the genus *Gossypium* are known as cotton, which is grown primarily for the seed hairs that are made into textiles. Cotton is predominantly used as a textile fiber because the mature dry hairs twist in such a way that fine, strong threads can be spun from them. Other products, such as cottonseed oil, cake, and cotton linters are byproducts of fiber production. Cotton is a perennial plant cultivated as an annual.

Taxonomy of Cotton

The genus *Gossypium*, a member of the Malvaceae, consists of 39 species, four of which are generally cultivated. The most commonly cultivated species is *G. hirsutum* L.; the others are *G. arboreum* L., *G. barbadense* L., and *G. herbaceum* L.

Genetics of Cotton

At least seven genomes, designated A, B, C, D, E, F, and G, are found in the genus. Diploid species ($2n = 26$) are found on all continents, and a few are of some agricultural importance. The A genome is restricted in diploids to two species (*G. arboreum* and *G. herbaceum*) of the Old World. The D genome is restricted in diploids to some species of the New World, such as *G. thurberi*.

By far the most important agricultural cottons are *G. hirsutum* and *G.barbadense*. These are both allotetraploids of New World origin and presumably of ancient cross between Old World A genomes and New World D genomes. How and when the original crosses occurred have been subject to much speculation. Euploids of these plants have 52 somatic chromosomes and are frequently designated as AADD. Four additional New World allotetraploids occur in the genus, including *G. tomentosum*, a native of Hawaii. *Gossypium tomentosum* has been crossed with *G. hirsutum* in breeding programs.

The New World allotetraploids are peculiar in the genus, because the species, at least in their wild forms, grow near the ocean as invaders in the constantly disturbed sandy habitats and associated environs. It is from these "weedy" or invader species that the cultivated cottons developed.

Pollination of Cotton

Gossypium hirsutum is generally self-pollinating, but in the presence of suitable insect pollinators can exhibit cross-pollination. Bumble bees (*Bombus* spp.), Melissodes bees, and honey bees (*Apis mellifera*) are the primary pollinators. Concentration of suitable pollinators varies from location to location and by season and is considerably suppressed by insecticide use. If suitable bee pollinators are present, distribution of pollen decreases considerably with increasing distance. In an experiment in which a cotton field was surrounded by a large number of honey bee colonies and movement of pollen was traced by means of fluorescent particles, 1.6 % of the flowers on plants 150 to 200 feet away showed the presence of the particles.

Gossypium tomentosum seems to be pollinated by lepidopterans, presumably moths. The stigma in *G. tomentosum* is elongated, and the plant seems incapable of self-pollination until acted upon by an insect pollinator. The flowers are unusual too, because they stay open at night. Most *Gossypium* flowers are ephemeral: They open in the morning and wither at the end of the same day.

Weediness

Although the New World allotetraploids show some tendencies to "weediness," the genus shows no particular weedy aggressive tendencies.

Modes of Gene Escape

Genetic material of *G. hirsutum* may escape from a test area by vegetative material, by seed, or by pollen. Propagation by vegetative material is not a common method of reproduction of cotton. Physical safeguards that inhibit the movement of vegetative material from the area should be adequate to prevent gene movement by this means. Movement of seed from the test area can likewise be inhibited by adequate physical safeguards.

Movement of genetic material by pollen is possible only to those plants with the proper chromosomal type. Movement to *G. hirsutum* and *G. barbadense* is possible if suitable insect pollinators are present and if there is a short distance from transgenic plants to recipient plants. Physical barriers, intermediate pollinator-attractive plants, and other temporal or biological impediments would reduce the potential for pollen movement.

Movement of genetic material to *G. tomentosum* is less well known. The plants are chromosomally compatible with *G. hirsutum*, but there is some doubt about the possibility for pollination. The flowers of *G. tomentosum* seem to be pollinated by moths, not bees. And they are receptive at night, not in the day. Both these factors would seem to minimize the possibility of cross-pollination. However *G. tomentosum* may be losing its genetic identity from introgression hybridization of cultivated cottons by unknown means.

Soybean as a Crop

Importance of Soybean

Soybean, *Glycine max* (L.) Merr., combines in one crop both the dominant world supply of edible vegetable oil and the dominant supply of high-protein feed supplements for livestock. Other fractions and derivatives of the seed have substantial economic importance in a wide range of industrial, food, pharmaceutical, and agricultural products.

Taxonomy of Soybean Relatives

The soybean is a papilionoid legume (family Fabaceae, subfamily Faboideae), and a member of the tribe Phaseoleae, subtribe Glycininae. The subtribe to which soybean belongs consists of 16 genera, none of which, except soybean (*Glycine*) and kudzu (*Pueraria*), are commonly known outside of botanical science. The genus *Glycine* is unique within the subtribe on several morphological and chromosomal characters, and does not seem to bear an especially intimate relationship with any other genus in the subtribe. A single exception may be the genus *Sinodolichos*, a rarely collected and poorly known genus from Asia. *Sinodolichos* is unknown in the living state outside of Asia.

The genus *Glycine* is divided into two questionably distinct subgenera: *Glycine* and *Soia*. The first consists of six or seven perennial species primarily from Australia. The second consists of three annual species from Asia: *Glycine max, Glycine soia* Sieb. & Zucc., and *Glycine gracilis* Skvortz. The first species is the cultivated soybean, the second species is the wild form of the soybean, and the third species is the weedy form of the soybean.

Morphology and Sexual Reproduction

The soybean plant is a branched, non-frost-tolerant annual about one meter above ground level and two meters below ground level. The stem tissues are mostly primary, although the basal and more mature portions of the stems develop secondary vascular tissues during later development. This woody development is in accord with the derivation of soybean from tree ancestors in the rosewood tribe, Dalbergieae. The nodulated root system is intermediate between a taproot type and a diffuse type. The foliage leaves are alternate, pinnately trifoliolate, with pulvini, stipels, and stipules.

The soybean flower is a standard papilionaceous flower with calyx of five united sepals; zygomorphic corolla of carina, alae, and vexillum; androecium of ten diadelphous 9+1 stamens; and gynoecium of a single carpel. Two to four seeds develop in the pods. The seeds have two large cotyledons and scant endosperm.

The anthers mature in the bud and shed their pollen directly onto the stigma of the same flower, thus ensuring a high degree of self-pollination. Cross-pollination is less than 1%, often substantially so. Soybean plants are thus virtually pure breeding homozygous lines, although manual cross-pollination is practiced routinely in breeding programs.

Distribution of Soybean

The United States, Brazil, China, and Argentina account for more than 90% of world soybean production. Soybeans are grown throughout much of the United States. The wild and weedy forms of soybean (*G. gracilis* and *G. soia*) and all other nonsoybean species of *Glycine* grow naturally only in Asia, Australia, and closely associated areas. In the United States, the wild and weedy forms of soybean are only known at university and other specialized research stations.

Modes of Gene Escape

Pollen is unlikely to escape from research plots. Soybeans are almost completely self-pollinated. Studies have shown that honey bees are responsible for the occasional cross-pollination and that thrips are ineffective pollination vectors. Certified Seed Regulations (U.S.) recognize this cross-pollination unlikelihood in the safeguards set up for Foundation, Registered, and Certified seed. For Foundation seed, the most stringent category in the Certified Seed Regulations, soybeans are permitted to be grown zero distance from the nearest contaminating source (i.e., other soybean cultivars), as long as the distance is adequate to prevent mechanical mixing.

Soybean seed has a short time potential for high germination and vigor, and, in commercial operation, fresh soybean seed is produced annually for each new season. However, some remaining seed from one crop is capable of germinating the following season and is therefore able to cause a temporal, if not geographic, dispersal of the soybean plant. Certified Seed Regulations stipulate that at lease one year must elapse between the destruction of a stand of soybean and a subsequent establishment of a new soybean stand. Vegetative reproduction of soybean plants does not occur under field conditions.

Maize as a Crop

Zea mays Linnaeus, known as maize throughout most of the world, and as corn in the United States, is a large, annual, monoecious grass that is grown for human consumption, animal feed, silage, vegetable oil, sugar syrups, and other miscellaneous uses. Maize has been cultivated since earliest historic times from Peru to central North America. The region of origin is now presumed to be Mexico. Dispersal to the Old World is generally deemed to have occurred in the sixteenth and seventeenth centuries; however, recent evidence indicates that dispersal to India may have occurred before the twelfth and thirteenth centuries by unknown means. In Africa, maize is a primary human food source and is grown throughout the continent wherever soils and water permit its cultivation. Cultivation is generally in small plots around rural villages, often interspersed with other food crops. Villagers mostly use landraces and keep seed from year to year to provide planting material for subsequent seasons. Maize is grown commercially as a row crop of monocultures of uniform plants from hybrid seed. Agronomic practices have developed a high degree of scientific sophistication in the use of tillage, pesticides, planting, fertilizer, harvesting, distribution, and all other agronomic aspects.

Taxonomy of Maize

Zea is a genus of the family Gramineae (Poaceae), commonly known as the grass family. The genus consists of some four species: *Zea mays*, cultivated maize and teosinte; *Zea diploperennis* Iltis et al., diploperennial teosinte; *Zea luxurians* Bird; and *Zea perennis* Reeves et Mangelsd., perennial teosinte. Various of the species have been assigned to the segregate genus *Euchlaena*, which is not currently recognized, or have been divided into numerous small species within the genus *Zea*.

The closest generic relative to *Zea* is *Tripsacum*, a genus of seven species. *Tripsacum* differs from maize in many respects, including chromosome number ($n = 9$), in contrast to *Zea* ($n = 10$). All species of *Tripsacum* can cross with *Zea*, but only with difficulty and only with extreme sterility.

Cultivated maize is presumed to have been transformed from *teosinte, Zea mays* subspecies mexicana (Schrader) Iltis, more than 8,000 years ago. During this transformation, cultivated maize gained several valuable agronomic traits, but lost the ability to survive in the wild. *Teosinte*, however, remains a successful wild grass in Mexico and Guatemala. Despite some confusion over proper taxonomic groupings of the noncultivated members of *Zea*, wild members maintain a successful array of annual or perennial plants with visible chromosomal peculiarities and ploidy levels, and many adaptive macroscopic phenotypes. Cultivated maize and the wild members of diploid and tetraploid *Zea* can be crossed to produce fertile F1 hybrids. Nonetheless, in the wild, introgressive hybridization does not occur because of differences in flowering time, geographic separation, block inheritance, developmental morphology, and timing of the reproductive structures, dissemination, and dormancy.

Morphology and Reproduction

Maize is a tall, robust, monoecious annual with overlapping sheaths and broad, conspicuously distichous blades; staminate spikelets in numerous long spike-like racemes forming large spreading terminal panicles (tassels); pistillate inflorescence in the axils of the leaves, the spikelets in 8–16 (30) rows, on a thickened, almost woody axis (cob), the whole enclosed in numerous large foliaceous bracts or spathes, the long styles (silk) protruding from the summit as a mass of silky threads; grains at maturity greatly exceeding the glumes. Pollination, fertilization, and caryopsis development of maize follows a fairly standard pattern for chasmogamous wind-pollinated grasses, with the following points of exception and note:

- Pollen is produced entirely in the staminate inflorescences. Eggs are produced entirely in the pistillate inflorescences.
- Self-pollination and fertilization and cross-pollination and fertilization are usually possible, and frequencies of each are usually determined by physical proximity and other physical influences on pollen transfer. A number of complicating factors, such as genetic sterility factors and differential growth rates of pollen tubes, may also influence the frequencies of self-fertilization versus cross-fertilization.
- The "silk" on a developing ear is the style, a part of the female flower through which a pollen grain must travel; the styles on maize are the longest known in the plant kingdom.
- Shed pollen typically remains viable for 10 to 30 minutes, but may remain viable for much longer under refrigerated conditions.
- The staminate and pistillate inflorescences do not develop at the same time. The pistillate inflorescence is precocious. However, there is the appearance of slight rotandry because the elongating styles are delayed for about seven days in emergence from the bracts of the pistillate inflorescence, while the development of the later-developing staminate inflorescence is fully visible.
- The genetics of maize are better known than those of any other crop plant.

Pollination of Maize

Studies of pollination of maize have mostly centered on the needs of hybrid seed production. This production involves the development and maintenance of inbred lines and the subsequent crosses to produce commercial seed. In the former, self-pollination is mandatory. In the latter, cross-pollination is mandatory. Mechanisms have been developed to ensure each kind of pollination.

Breeder seed is usually derived from self-pollinated seed at the F8 to F10 generation of inbreeding. A high degree of self-pollination is ensured by planting well-isolated blocks that virtually guarantee natural random sib mating. Minimum isolation distances for foundation seed are one-eighth mile (660 feet) from the nearest contaminating source. Other safeguards, such as physical barriers or unharvested border rows, can further reduce the possibility of contamination. Fields are preferred that have not been recently planted in maize. This is to minimize the appearance of volunteer maize from a previous season.

Hybrid seed production fields also require isolation, similar to that for foundation seed. Isolation distance may be modified by such factors as high winds, additional border rows, size of field, natural barriers, and differential flowering dates. Flowering dates are often adjusted by differential planting dates, planting depth, or fertilizing. The two different parents are planted in a regular pattern of rows, such as four pistillate to one staminate (4:1), or 4:2, or 6:2, or a variety of other combinations. Detasseling or use of cytoplasmic male sterility prevents pistillate plants from shedding viable pollen and thus ensures cross-pollination.

Weediness

Maize appears as a volunteer in some fields and roadsides, but it never has been able to establish itself outside of cultivation. Some of the other species of *Zea* are successful wild plants but have no pronounced weedy tendencies.

Modes of Gene Escape

Genes of maize may escape from the test plot in two ways. The first is by pollen transfer. The second is by movement of the grain.

If viable pollen of the transgenic plants can be transferred by wind to any receptive maize stigma within the 30-minute period of pollen viability, an escape of genetic material could take place. This potential transfer becomes more unlikely as distance increases from the transgenic plants, and from a practical standpoint becomes increasingly unlikely at distances much beyond the foundation seed isolation distance of 660 feet. Temporal isolation would further reduce the likelihood of effective pollination and fertilization. In addition, any physical impediment to this movement, such as effective detasseling or bagging, would completely eliminate the possibility of gene escape by way of pollen.

To prevent grain from remaining in the field or otherwise escaping, all ears would have to be collected or otherwise destroyed. To ensure that no grain escaped harvest, the field would have to be monitored for volunteer maize plants in the following season.

PART THREE

Appendixes

APPENDIX 1: Glossary of Terms

Agrobacterium (a) A soil bacterium that can be used to transfer DNA genes into plants; (b) a genus of bacteria that includes several plant pathogenic species that cause tumor-like symptoms.

antibiotic-resistance (marker) gene (a) A bacterial gene coding for a protein that confers resistance to one or more antibiotics (such as ampicillin or kanamycin), used to identify transformed cells in the laboratory phase of research; (b) a gene used as a selection marker to distinguish cells that have taken up foreign DNA from those that have not; its action allows cells to survive in the presence of normally toxic antibiotic agents. Biosafety concerns include potential toxicity or allergenicity of the resulting protein and possibility of horizontal transfer from food or animal feed products to microorganisms in the human or animal gut, or the environment, which may compromise the therapeutic efficiency of clinically useful antibiotics.

***Bacillus thuringiensis* (Bt)** A group of soil bacteria found worldwide that produce a class of proteins that are toxic to the larvae (caterpillars) of certain insects, particularly *Coleoptera* and *Lepidoptera*. Genes coding for Bt proteins are now commonly used to genetically engineer plants to resist insect attack; spores of Bt are a major means of insect control in organic farming.

biodiversity The total variability within and among species of living organisms and their habitats.

biosafety (a) The goal of ensuring that the development and use of genetically engineered organisms and products made from them do not negatively affect plant, animal, or human health; genetic resources; or the environment; (b) policies and procedures adopted to avoid risk to human health and safety, and to the conservation of the environment, as a result of the use of genetically modified organisms for research and commerce.

biotechnology (a) The scientific or industrial use of living organisms to make or modify new products or improve existing plants, animals, or microorganisms. The term applies to the technique of gene splicing and, more generally, to other modern technologies such as plant tissue culture, embryo transfer, cell fusion, and fermentation; (b) any technological application that uses biological systems, living organisms, or derivatives thereof to make or modify products or processes for specific use; (c) interpreted in a narrow sense, a range of different molecular technologies such as gene manipulation and gene transfer, DNA typing, and cloning of plants and animals.

Bt crop A crop plant genetically engineered to produce insecticidal proteins derived from the bacterium *Bacillus thuringiensis*.

center of diversity A location(s) having a significant genetic diversity of a particular species; often but not always the center of origin.

center of origin The place or region where a crop species is thought to have originated.

chromosome (a) A highly compact, thread and spool-like structure comprising a long DNA molecule and associated proteins on which thousands of genes are arranged in a linear sequence; (b) the nuclear bodies containing most of the genes largely responsible for the differentiation and activity of the eukaryotic cell. Each eukaryotic species has a characteristic number of chromosomes.

commercialization (a) Placing on the market; (b) large-scale planting or importation of a GM crop or ornamental or tree species for the purpose of export or sale to the public.

confinement Isolation of an organism from its environment, including other sexually compatible plants using biological, spatial, temporal, and genetic mechanisms, e.g., isolation by distance, male sterility.

construct (noun) (a) An engineered DNA fragment designed to be transferred into a cell or tissue. Typically the construct comprises the gene or genes of interest, a marker gene, and appropriate control sequences as a single package; (b) a piece of DNA that has been intentionally assembled from various DNA segments and that may code for a protein or regulate gene expression.

containment (a) Physical isolation of an organism from its environment; (b) measures and protocols applied to limit contact of genetically modified organisms or pathogens with the external environment; (c) use of physical means (e.g., greenhouses, indoor growth facilities, isolated locations) and/or biological methods (e.g., male sterility, flower removal) to ensure that neither the organism nor its genetic material (in the form of propagative structures, seeds, pollen) is released into the environment.

deliberate release (a) Any intentional introduction into the environment of a GMO or a combination of GMOs for which no specific containment measures are used to limit their contact with and to provide a high level of safety for the general population and the environment; (b) any intentional use of organisms that is not under containment.

DNA Deoxyribonucleic acid; the material of which genes are made; a linear molecule consisting of a sequence of chemical subunits called bases, which encodes genetic information in the sequence of bases. It is present in chromosomes in the cell nucleus and also in chromosomal material of subcellular units such as mitochondria and chloroplasts.

electroporation (a) Use of an electric shock to facilitate transfer of isolated DNA into recipient cells, one of several procedures used for transformation; (b) the induction of transient pores in bacterial cells or plant protoplasts by the application of a pulse of electricity. These pores allow the entry of DNA into the cell.

environmental risk assessment The evaluation of risks to human health and the environment, whether direct or indirect, immediate or delayed, that are posed by the deliberate release or placing on the market of GMOs.

field test Experimentation with crops in a field situation to evaluate phenotypic traits, agronomic performance, and other parameters of interest.

gene (a) The physical and functional unit of heredity transmitted from generation to generation during sexual and asexual reproduction; (b) a linear segment of DNA that is made up of an ordered sequence of nucleotide bases that specifies the structure of a protein or has an defined function. More generally, the term is used in relation to the transmission and inheritance of particular identifiable traits.

gene flow (a) The exchange of genes in one or both directions at a low rate between different (usually) related and sexually compatible populations of organisms; (b) the horizontal movement of genes via pollen transfer among related or even unrelated plant species; (c) the spread of genes from one breeding population to another population.

genetic engineering See *genetic modification.*

genetic modification (a) Modifying an organism's genetic makeup by the introduction of a gene or genes into its cells in a way that allows transfer of the gene to successive generations; (b) the process of intentionally altering the genetic makeup of an organism, usually by insertion of one or more genes and/or regulatory sequences that may come from the same or any other organism. Modern biotechnology is used to alter the genetic material of living cells or organisms in order to make them capable of producing new substances or performing new functions.

genetically modified organism (GMO) (a) The broad term used to identify organisms in which the genetic material has been altered by use of molecular techniques (i.e., in a way that does not occur naturally by mating and/or natural recombination); (b) an organism that has been transformed by the insertion of one or more genes.

genome The entire complement of genetic material present in each cell of an organism.

GM product A preparation consisting of or containing a GMO or a combination of GMOs that is placed on the market.

hazard The potential of an organism to cause harm to human health and/or the environment; may also be referred to as "adverse effect."

hybrid The offspring of genetically different parents.

organism Any biological entity able to replicate or transfer its own genetic material.

phenotype (a) The visible or measurable qualities of an organism as distinguished from its genetic constitution (genotype); (b) the visible appearance of an individual that reflects the reaction of its genome with a given environment.

promoter (a) A short DNA sequence to which RNA polymerase and certain regulating molecules bind to initiate synthesis from a DNA template (gene); (b) a DNA sequence associated with a gene that determines under what conditions that gene is expressed. Promoters may be: (1) *tissue-specific*, meaning they determine that the gene will be expressed only in e.g., seeds or leaves or roots, etc.; (2) *inducible*, meaning the gene will be expressed only in response to an external trigger such as exposure to insect attack, heat, etc.;(3) *developmentally specific*, meaning the gene will be expressed only at certain stages of development, such as in embryos or during flowering or in senescing organs; (4) *constitutive*, meaning the gene will be expressed under virtually all conditions.

risk The combination of the magnitude of the consequences of a hazard, if it occurs, and the likelihood that the consequences will occur.

risk assessment The measures to estimate what harm might be caused, how likely it would be to occur, and the scale of the estimated damage.

risk communication (1) The science of understanding scientific and technological risk and how it is communicated within a socio-political structure (Dr. Vincent Covello); (2) the presentation of information, sometimes technical in nature, regarding risk — its nature, magnitude, likelihood, consequences, management, etc. — in a manner that is accessible and understood by a nontechnical audience.

risk management The measures to ensure that the production and handling of an organism are safe.

stakeholder (1) A person or group that has an investment, share, or interest in something, such as a business or industry; (2) somebody or something with direct interest — a person or group with a direct interest, involvement, or investment in something, for example, the employees, shareholders, and customers of a business concern.

toxin A biological compound produced by one organism that is deleterious to the growth and/or survival of another organism.

transformation (a) The uptake and integration of DNA in a cell in which the introduced DNA is intended to change the recipient organism in a predictable manner; (b) the introduction and assimilation of DNA from one organism by another.

transgene A gene that has been introduced into a genetically modified or transformed organism.

transgenic (organism) (a) An organism in which one or more new genes ("transgenes") have been integrated into its genome by genetic modification; includes the offspring of a genetically modified organism.

vector A self-replicating agent (for example, a plasmid or virus) used to deliver DNA into a cell.

weediness The plant phenotype of interfering with human activities, being a nuisance in agronomic settings, and/or disrupting native ecosystems. A plant may be designated a weed based on various traits, some of which may be subjective, such as rapid growth, invasiveness, persistence, pest and disease resistance, high reproductive capacity, and causing reduced crop yields.

APPENDIX 2: Annotated List of Internet Sites

General Information

AgBiosafety

http://www.agbiosafety.unl.edu

A source of scientific, regulatory, and educational materials relevant to crop biotechnology and the current debate on the genetic modification of food. The site offers up-to-date information on current issues in biotechnology and food safety and a searchable database of safety information on GM crops that have received regulatory approval in Canada, the United States, and elsewhere. It provides educational resources and lesson plans on crop biotechnology for both consumers and educators and links to other biotech education sites.

AgBiotechNet

http://www.agbiotechnet.com

Ag BiotechNet covers all aspects of the application of biotechnology and genetic engineering in agricultural production and food processing and marketing. The focus is on scientific reports and findings and technical analysis, although the site also covers emerging issues of widespread interest, developments in the policy arena, and major media coverage.

AgBioWorld

http://www.agbioworld.org

Devoted to bringing information about technological advances in agriculture to the developing world; provides information to teachers, scientists, journalists, and the general public on the relevance of agricultural biotechnology to sustainable development; maintains the declaration of "Scientists In Support Of Agricultural Biotechnology," and offers a discussion listserve.

Biotechnology Australia

http://www.biotechnology.gov.au

Biotechnology Australia is a multidepartmental government agency responsible for coordinating nonregulatory biotechnology issues for the Commonwealth Government. It seeks to provide balanced and factual information on biotechnology to the Australian community.

NOTE: The Web addresses in this list were correct as of July 2002. Given the dynamic nature of the Internet, over time some sites may be moved to a new address, become inactive, or closed.

Checkbiotech

http://www.checkbiotech.org

The aim of this site, sponsored by Syngenta, is to provide trustworthy and up-to-date information on agricultural biotechnology and thereby to contribute to an open debate. The collection of documents gives an overview of ongoing discussions in agricultural biotechnology. The information provided comes from different sources and thus may not always reflect the opinion of the sponsor. This site will be useful for people with a special interest in the field of ag-biotech and GM-food, primarily opinion makers and decision makers around the globe. It also serves as an informational and educational tool for the general public and for schools.

Council for Biotechnology Information

http://www.whybiotech.com

This site carries extensive information organized in sections for consumers, farmers, journalists, teachers, and students. Also found are up-to-date, in-depth reports, publications, and news articles.

Information Systems for Biotechnology (ISB)

http://isb.vt.edu

Here you will find documents and searchable databases pertaining to the development, testing, and regulatory review of genetically modified plants, animals, and microorganisms within the United States and abroad.

Life Sciences Knowledge Center (Monsanto)

http://www.biotechknowledge.monsanto.com

This site maintains an evolving collection of news items, technical reports, and other documents representing many points of view on agricultural biotechnology; sections on biotechnology basics, glossary, topic library, and a discussion board.

Transgenic Crops: An Introduction and Resource Guide

http://www.colostate.edu/programs/lifesciences/TransgenicCrops

This Colorado State University site provides broad coverage of the subject, including the history of plant breeding, a clear explanation of what transgenic plants are and how they are made, biosafety evaluation and regulation, current and future transgenic products, and a question-and-answer format for information on risks and concerns.

International Organizations and Programs

Agricultural Biotechnology Support Project (ABSP)

http://www.iia.msu.edu/absp

ABSP is a project funded by the U.S. Agency for International Development based in the Institute for International Agriculture at Michigan State University. The project, which began in 1991, aims to assist developing countries in the development and management of the tools and products of agricultural biotechnology.

BIO-EARN – East African Regional Programme and Research Network for Biotechnology, Biosafety and Biotechnology Policy Development

http://www.bio-earn.org

The overall objectives of the BIO-EARN Programme are to: enable countries in the region to develop biotechnologies and policies according to their own needs, abilities, and opportunities; promote collaboration in biotechnology, biosafety, and biotechnology policy development to address key challenges and opportunities in the region; and foster communication nationally and regionally between scientists, policy makers, biosafety regulatory officials, and private sector.

Biosafety Information Network and Advisory Service (BINAS)

http://www.binas.unido.org/binas

BINAS, a service of the United Nations Industrial Development Organization (UNIDO), monitors global developments in regulatory issues in biotechnology providing information on worldwide national regulations and field trials.

Biotechnology Advisory Center (BAC) (Stockholm Environment Institute)

http://www.sei.se/biotech/bac.html

The BAC was established to help meet the challenge of biosafety capacity building in developing countries. The BAC's support consists of three components: training, independent advice, and biosafety and biotechnology information exchange. The East African Regional Programme and Research Network for Biotechnology, Biosafety and Biotechnology Policy Development (BIO-EARN) is the main activity at present. The principal objective of the BIO-EARN programme is to build national capacity and competence in biotechnology, biosafety, and biotechnology policy. Selected academic and governmental institutions in Ethiopia, Kenya, Tanzania, and Uganda will receive support through a regional network.

BioTrack Online

http://www.oecd.org/EN/home/0,,EN-home-528-nodirectorate-no-no-no-27,FF.html

BioTrack Online was created in 1995 as a pioneer site at the Organization for Economic Cooperation and Development (OECD) in the field of the safety in biotechnology. This site focuses on information related to the regulatory oversight of products of biotechnology. BioTrack Online currently includes: information related to major legislative developments in OECD member countries (including details of the relevant regulatory authorities); an online database of products of biotechnology as well as field trials; a number of free documents; and links to other related Web sites. BioTrack is used by governments, industry, other stakeholders, and all who need the information in the field.

CamBioTec

http://www.promega.com/latinamerica/cambiotech.htm

CamBioTec is an international network with the mission to facilitate biotechnology-based applications in the fields of agri-food and environmental management in Latin America by promoting a favorable environment for the development of the industry, and by increasing public awareness on the associated benefits and eventual risks.

Cartagena Protocol on Biosafety (CBP)

http://www.biodiv.org/biosafety

This is the main site for information about the CPB, including the background and full text of the agreement, articles, updated list of signatures and ratifications, meetings, and documents of the Intergovernmental Committee for the Cartagena Protocol (ICCP), the Biosafety Clearing House, and a database of biosafety capacity-building activities.

International Centre for Genetic Engineering and Biotechnology (ICGEB)

http://www.icgeb.trieste.it/~bsafesrv

The Biosafety Unit of the ICGEB is dedicated to biosafety and risk assessment for the environmental release of genetically modified organisms. It offers information on biosafety concerns, upcoming meetings and training courses, and a regularly updated index of selected scientific articles published on biosafety and risk assessment from 1990 onward. This site also carries an outstanding collection of links to databases on GMO releases, scientific bibliographies, decision support systems, patents, and numerous other topics.

International Service for the Acquisition of Agri-biotech Applications (ISAAA)

http://www.isaaa.org

The primary site describes ISAAA's activities and initiatives in biosafety, food safety, intellectual property, and technology transfer. The Global Knowledge Center on Crop Biotechnology section (*http://www.isaaa.org/activities/knowledge_center.htm*) is organized into several main areas. Global Network provides a status of biotechnology in the developing countries of Asia, South America, and Africa. Crop Biotech Update is a weekly summary of world developments in agricultural biotechnology for developing countries. Separate pages cover GM products and biotechnology issues. ISAAA is a not-for-profit international organization co-sponsored by public and private sector institutions with the aim of facilitating the acquisition and transfer of agricultural biotechnology applications from the industrial countries, particularly proprietary technology from the private sector, to developing countries for their benefit.

UNEP-GEF Biosafety Project

http://www.unep.ch/biosafety

The UNEP-GEF Biosafety Project is funded by the Global Environmental Facility and is based on its "Initial Strategy for assisting countries to prepare for the entry into force of the Cartagena Protocol on Biosafety" (GEF/C.16/4). The main objectives of this strategy are to assist countries in the establishment of their national biosafety frameworks; promote information sharing and collaboration, especially at the regional and subregional level; and promote collaboration with other organizations to assist capacity-building for the the Cartagena Protocol on Biosafety.

National Biosafety Agencies

Australia: Office of the Gene Technology Regulator (OGTR)

http://www.health.gov.au/ogtr

The OGTR was established in 2000 to be responsible for a national scheme to regulate genetically modified organisms. The new Gene Technology Technical Advisory Committee will provide expert scientific advice on applications for contained research, field trials, and general releases involving GMOs. The scientific committee will also provide advice on other matters related to gene technology, GMOs, and GM products and on the need for, and proposed content of, policy principles, policy guidelines, codes of practice, and technical and procedural guidelines for GMOs and GM products.

Belgium: Biosafety Server

http:// biosafety.ihe.be

This site is run by the Service of Biosafety and Biotechnology (SBB) and hosted by the federal Scientific Institute of Public Health under the Belgian Ministry for Consumer Protection, Public Health and Environment. It contains regulatory information for Belgium, Europe, and other countries; risk-assessment data; biosafety related meetings, conferences, and courses.

Canada: Canadian Food Inspection Agency

http://www.inspection.gc.ca/english/ppc/biotech/bioteche.shtml

The Canadian Food Inspection Agency (CFIA) is responsible for the regulation of products derived through biotechnology including plants, animal feeds and animal feed ingredients, fertilizers, and veterinary biologics. For genetically modified crop plants, the CFIA assesses the potential risk of adverse environmental effects and authorizes and oversees import permits, confined trials, unconfined release, and variety registration.

United Kingdom: Advisory Committee on Releases to the Environment (ACRE)

http://www.defra.gov.uk/environment/acre

ACRE, a nondepartmental public body, advises the Department for Environment, Food and Rural Affairs on applications to field test or release for commercial use agricultural GMOs. The site has extensive background information on the release of GMOs in the European Union, lists of applications for experimental trials and to market GMOs, application formats for deliberate releases and marketing of higher plants and organisms other than higher plants, a statement on GM animals, and more. The Guidance on Principles of Best Practice in the Design of Genetically Modified Plants documents how the design and construction of GM plants could be used to further improve their safety and/or to simplify the risk assessment.

United States: Department of Agriculture Animal and Plant Health Inspection Service (APHIS)

http://www.aphis.usda.gov/biotech

This Web site contains detailed information on how the U.S. Department of Agriculture's Animal and Plant Health Inspection Service (APHIS) regulates the movement, importation, and field testing of genetically modified plants and microorganisms through permitting and notification procedures. It links to other sites containing information on permits for other types of genetically modified organisms or products such as transgenic arthropods and veterinary biologics.

United States: Regulatory Oversight of Biotechnology

http://www.aphis.usda.gov/biotech/usregs.htm

This site is a portal to the agencies primarily responsible for regulating biotechnology: the U.S. Department of Agriculture (USDA), Environmental Protection Agency (EPA), and the Food and Drug Administration (FDA). Products are regulated according to their intended use; some products are regulated under more than one agency.

Field Test Information

BioBin

http://www.oecd.org/ehs/biobin

BioBin is a cooperative resource on safety in biotechnology developed between OECD's BioTrack Online and Biotechnology Information Network and Advisory Service (BINAS) sponsored by the United Nations Industrial Development Organization (UNIDO). A resource for regulations, field trials, biotechnology product database, biotechnology libraries, and tools related to biosafety.

International Field Test Web Sites

http://www.isb.vt.edu/cfdocs/globalfieldtests.cfm

This site is a list of links to information about field tests conducted in twenty-nine countries.

Organization for Economic Cooperation and Development (OECD) Database of Field Trials

http://www.olis.oecd.org/biotrack.nsf

This database includes records of field trials of genetically modified organisms that have taken place in OECD member countries. It also includes data from other countries that have been provided through UNIDO's BINAS.

Food Safety

Canada Food Inspection Agency

http://www.inspection.gc.ca/english/toc/bioteche.shtml

This site carries comprehensive information about the structure and operations of Canada's regulatory framework for biotech foods, consumer information, technical reports, and more.

Codex Alimentarius

http://www.codexalimentarius.net

The Codex Alimentarius, or the food code, has become the seminal global reference point for consumers, food producers and processors, national food control agencies, and the international food trade. Codex standards have become the benchmarks against which national food measures and regulations are evaluated. This site carries provisional agendas for forthcoming meetings and working papers and reports of Codex Meetings. Of particular interest is the Preliminary Report of the ad hoc Intergovernmental Task Force on Foods Derived from Biotechnology (final report due in 2003).

Food and Agriculture Organization (FAO) of the United Nations

http://www.fao.org/biotech/index.asp?/lang=en

This site on food and agriculture is available in Arabic, French, Chinese, Spanish, and English. It carries news and events, FAO documents, sectoral overviews, and a glossary (English only).

Food Products Unit (FPU)

http://food.jrc.it

The FPU of the European Commission's Joint Research Council works in two main areas: activities within the field of food safety and quality, and issues on genetically modified organisms. The unit's main clients and partners are the European Commission Directorates involved in establishing legislation related to food and feed. Other aspects of the unit's work are harmonization of analytical procedures in order to produce reliable data for risk assessment, detection of fraud, and monitoring of compliance with labeling regulations.

Health Canada Food Program: Novel Foods

http://www.hc-sc.gc.ca/english/protection/novel-foods.html

Information on Canada's food safety reviews and decisions of GM commodities. This site also has GM food fact sheets and frequently asked questions about biotechnology and GM foods.

Institute of Food Technologists (IFT)

http://www.ift.org

The Institute of Food Technologists advances the science and technology of food through the exchange of knowledge. This site features the Biotech Board, weekly newsletter, related links, information about membership and benefits, meetings and training opportunities, and a wealth of additional information.

International Food Information Council (IFIC) Foundation

http://ific.org./food/biotechnology.vtml

The purpose of the IFIC Foundation, a nonprofit organization based in Washington, D.C., is to provide sound, scientific information on food safety and nutrition to journalists, health professionals, educators, government officials, and consumers. This link connects to the section on food biotechnology.

U.S. Center for Food Safety and Applied Nutrition (CFSAN)

http://vm.cfsan.fda.gov/~lrd/biotechm.html

CFSAN, in conjunction with the field staff of the U.S. Food and Drug Administration, is responsible for promoting and protecting the public's health by ensuring that the nation's food supply is safe, sanitary, wholesome, and honestly labeled, and that cosmetic products are safe and properly labeled.

U.S. Food and Drug Administration (FDA): Biotechnology

http://vm.cfsan.fda.gov

The FDA regulates foods and feed derived from new plant varieties (GMOs) as well as conventional products. The biotechnology site carries extensive documentation on regulations, labeling, consumer information, and products approved for commercial sale.

World Health Organization (WHO) – Biotech Foods

http://www.who.int/fsf/GMfood/index.htm

WHO has been addressing a wide range of issues in the field of biotechnology and human health, including safety evaluation of vaccines produced using biotechnology, human cloning, and gene therapy. This site briefly describes the activities of WHO in regard to biotechnology and food safety.

Commentary / Expert Opinion

Ag Biotech Infonet

http://www.biotech-info.net

This site carries commentary on a wide variety of genetic engineering topics. Articles gleaned from newspapers and magazines around the world cover, for example, current uses for insect and disease resistance, herbicide tolerance and other traits, costs and benefits, environmental impacts, policy, and more.

Center for International Development, Harvard University

http://www.cid.harvard.edu/cidbiotech

This site includes background papers and a forum to promote exchange of views on topical issues related to biotechnology and development. These include: the evolution of the biotechnology industry; biotechnology in international trade; intellectual property rights in biotechnology; biotechnology and international relations; bio-prospecting; biotechnology in developing countries; environmental aspects of biotechnology; biotechnology and human health; and ethics, social values, and biotechnology.

Council for Agricultural Science and Technology (CAST)

http://www.cast-science.org

CAST assembles, interprets, and communicates science-based information regionally, nationally, and internationally on food, fibre, agricultural, natural resources, and related societal and environmental issues to stakeholders—legislators, regulators, policy makers, the media, the private sector, and the public.

International Life Sciences Institute (ILSI)

http://www.ilsi.org/site_search/index.cfm

ILSI is a nonprofit, worldwide scientific research foundation seeking to improve the well-being of the general public through the pursuit of sound and balanced science. Its goal is to further the understanding of scientific issues relating to nutrition, food safety, toxicology, risk assessment, and the environment. This site lists ILSI publications pertaining to biotechnology.

Public Perception

Center for Consumer Research, University of California–Davis

http://ccr.ucdavis.edu

This site focuses on consumer attitudes toward food safety and quality. It includes an informative section defining biotechnology and some current issues. A "Biotechnology Message Board" allows for questions and answers.

Electronic Forum on Biotechnology in Food and Agriculture

http://www.fao.org/biotech/forum.htm

This site provides an open forum that will allow a wide range of parties, including governmental and nongovernmental organizations, policy makers, and the general public, to discuss and exchange views and experiences about specific issues concerning biotechnology in food and agriculture for developing countries.

European Federation of Biotechnology (EFB) Agri-Biotechnology (Europe)

http://www.agbiotech.org

The EFB is an association of European scientific and technological societies in biotechnology together with universities, scientific institutes, companies, biotechnology associations, and individual members. Their mission is ". . . to promote the safe, sustainable, and beneficial use of Nature's resources in the life sciences and technologies; to facilitate exchange of people and ideas; and to contribute to a better understanding and perception of biotechnology by the general public in Europe."

European Federation of Biotechnology (EFB) Task Group on Public Perceptions of Biotechnology

http://www.efbpublic.org

This group works to increase public awareness and understanding of biotechnology and the life sciences throughout Europe, to advance the public debate about their applications, and to facilitate dialogue between interested parties. The site's primary aim is to foster greater public awareness and understanding of biotechnology and to encourage public debate.

Food Future: Genetically Modified Crops and the Environment (United Kingdom)

http://www.foodfuture.org.uk

The Food and Drink Federation's Food Future program aims to improve public understanding of genetic modification. The program has initiated wider discussion of the technology — the perceived benefits and disadvantages as well as the ethical and moral concerns. The site provides consumers with facts and figures about GM crops so that they can make informed decisions about what they buy. The site has informative sections on the benefits, risks, and regulation of GM crops in the United Kingdom.

Genetically Engineered Organisms – Public Issues Education Project (GEO-PIE)

http://www.comm.cornell.edu/gmo/gmo.html

GEO-PIE was developed at Cornell University to create objective educational materials exploring the complex scientific and social issues associated with genetic engineering to help readers consider those issues for themselves.

Publications

AgBioForum Magazine

http://www.agbioforum.org

AgBioForum publishes articles that enhance the on-going dialogue on the economics and management of agricultural biotechnology. The purpose of *AgBioForum* is to provide unbiased, timely information and new ideas leading to socially responsible and economically efficient decisions in science, public policy, and private strategies pertaining to agricultural biotechnology.

Bioline International Biosafety Journal Online

http://bioline.bdt.org.br/by

This free site provides peer reviewed journals containing papers on the effects of GMOs and introduced species on people and the environment, and other materials in biotechnology, biodiversity, environmental and ecological sciences, food/agriculture/veterinary science, medicine, microbiology, and taxonomy.

Biotechnology and Development Monitor

http://www.biotech-monitor.nl

The *Monitor* provides a forum for discussion on the positive and/or negative impact of biotechnological innovations and international regulations on issues such as economic growth, agricultural production, food security, shifts in national and global markets, access to technology, employment, social differentiation, and human rights. The analyses are interdisciplinary and emphasize the integration of theoretical and empirical information from social sciences and natural sciences.

Environmental Biosafety Journal

http://www.edpsciences.org/ebr

Environmental Biosafety Research (EBR) is a new interdisciplinary, international journal that publishes the results of research related to science-based risk-assessment of GMOs. Included are peer-reviewed original research papers and review articles, as well as scientific correspondence on all types of GMOs, including plants, animals, and microbes. The scope of material encompasses: ecological studies of the impact of novel organisms; studies of their interactions with pests and pathogens; food- and feed-safety evaluation; impact of novel organisms on agronomy and farming practice, effect on microbial populations; economic and sociological studies; means for reducing or managing risk; and assessment of horizontal gene flow.

Donors

McKnight Foundation, USA

http://www.mcknight.org

The mission of the McKnight Foundation is to improve the quality of life for present and future generations and to seek paths to a more humane and secure world. The foundation also hopes to contribute to food security by focusing attention on often-neglected crops and on issues involved in food security. Such issues include food storage, distribution, the dwindling supply of arable land, water shortages, agricultural education, indigenous farming practices, agricultural technology, and nutrition.

National Agricultural Biotechnology Council (NABC), United States

http://www.cals.cornell.edu/extension/nabc

The National Agricultural Biotechnology Council is a not-for-profit consortium of more than thirty leading agricultural research and teaching universities in the United States and Canada. The organization has been hosting annual public meetings about the safe, ethical, and efficacious development of agricultural biotechnology products since 1988. NABC continues to provide all stakeholders the opportunity to speak, to listen, and to learn about the issues surrounding agricultural biotechnology.

Novartis Foundation

http://www.foundation.novartis.com

The Novartis Foundation is engaged in programs in developing countries that directly contribute to an improvement in the quality of life of the poorest people. The Risk Fund, a fund for the promotion of creative and out-of-the-ordinary commercial projects and programs in developing countries is highlighted.

The Rockefeller Foundation, USA

http://www.rockfound.org

The Rockefeller Foundation seeks long-term, systemic, enduring change, and accomplishing that takes time—far longer than just one year. Grantmaking is organized around four thematic lines: creativity and culture, food security, health equity, and working communities. A cross-theme of global inclusion supports, promotes, and supplements the work of these themes. In addition, the foundation supports a number of programs that are developing or in transition.

Business/Professional Organizations

AfricaBio

http://www.africabio.com

AfricaBio seeks to promote the enhancement of the quality of life in Africa through the safe and responsible application of biotechnology. The site provides two e-publications: *BioLines* — AfricaBio's "Biotechnology Headlines" — and *MedBioLines*, which focuses on developments in medical and pharmaceutical biotechnology.

BIOTECanada

http://www.biotech.ca

This site was created to help people gain a better understanding of biotechnology and how it improves our quality of life. It represents Canadian health care, agricultural, food, research, and other organizations that are involved in biotechnology. BIOTECanada also offers a range of services to its members.

Biotechnology Industry Organization

http://www.bio.org

This organization is the largest trade organization to serve and represent the emerging biotechnology industry in the United States and around the globe. The site includes a media guide to biotechnology; a biotechnology food products list; a citizen's guide to biotechnology; laws and policies; and a guide to bioethics.

Council for Biotechnology Information

http://www.whybiotech.com

Called *Whybiotech*, the site provides objective, balanced information to help understand and appreciate the benefits that biotechnology offers, as well as to encourage informed debate about the issues it raises. The site includes recent news articles, essential background information, sections on the benefits and regulations of biotechnology, media and resource centers, frequently asked questions, links, and an events calendar.

EuropaBio

http://www.europabio.org

EuropaBio, the European Association for Bioindustries, represents nearly forty member companies operating worldwide and eighteen national biotechnology associations. This site features an "Info Kit" with nineteen modules on topics including an introduction to biotchnology, environmental effects and food safety of GM crops, and frequently raised arguments against biotechnology, commercial GM crops, industrial biotechnology, and others. It also carries the latest news reports and information on forthcoming events.

Miscellaneous

On-Line Courses in Biotechnology

http://project.bio.iastate.edu

Guided by faculty and administrators in seven departments and programs at Iowa State University, the program strives to develop and share biology education resources via the Internet.


ONIONS

APPENDIX 3: Sources and Suggested Reading

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